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Being serious about games

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BEING SERIOUS ABOUT GAMES

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Being serious about games;

Whether, how, why, and when computer- and game-based interventions could facilitate in reducing burdens of chronic somatic symptoms

Proefschrift

ter verkrijging van de graad van doctor aan Tilburg University
op gezag van prof. dr. G.M. Duijsters, als tijdelijk waarnemer van de functie rector magnificus en uit dien hoofde vervangend voorzitter van het college voor promoties, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie

in de Aula van de Universiteit
op donderdag 4 juli 2019 om 13.30 uur

door

Miel Antonius Petrus Vugts,
geboren te Breda

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“The mind is embodied, not embrained”

Antonio Damasio

Contents

Appendices S1 & S2 are available from the author

1 GENERAL INTRODUCTION

Broken
Once I was whole. No, better
than whole, possibilities
strewn at my feet, choices
all mine for the making.

Then I got sick, and broken.
Now I struggle to fly with broken wings.
Old ambitions and desires
irrelevant, crashing down
to earth with new humility.

Always aiming for superlatives,
now grounded with indistinction,
my new insignificance frees me
from the need to be special.

Now I struggle to run with broken legs.
Can't keep up, can't catch up,
and the world passes by oblivious
to my desperate thrashing.

All that's gained is lost
eventually. I jettison years
of accumulation, learn how much
I can do without, pare life down.

To bare essentials, and find
the remaining kernel sufficient,
my load much lightened and easy
to swing over obstacles ahead.

Now I struggle to live with a broken spirit.
This, I think, I cannot do.
I languish, lacking spur of vital impulse,
motivation crippled, desire withered.

Paralyzed by apathy, stubborn
hope insists, after broken wings
and broken legs, after the crash
and pain of loss comes possibility

For something new. Anchorless alone
I drift, restrain my swelling panic
at this formless space all around me,
No purchase to be gained on these

feeble clouds, nothing solid to push
either for or against – I struggle only
with myself. And in this void I must trust,
resist the urge to close, and endure,
with broken open heart.

By: Angelika Byczkowski, from: http://www.theunbrokensmile.com/poem-about-living-with-chronic-illness/

1.1 A SHORT IMPRESSION OF THE CENTRAL THEME

Dualistic thinking clashes with experiences of people living with chronic pain. In chronic pain, experiences of physical condition can become 'enmeshed' with identity and constantly demand sufferers´ attention [1, 2]. Both the poem by a patient living with a chronic pain condition and the quote by Antonio Damasio (p. 5), a neurologist studying human consciousness, suggest that body and mind are one. The work of Damasio and colleagues contested 'dualism', which is popularly traced back to Descartes' expression "I think and therefore I am", as well as reductionism as described with "I am my brain" [3]. Nonetheless, dualistic assumptions remain influential in supporting distinction between 'subjective' and 'objective', and placement of responsibility for health issues disproportionately at either 'agents' or 'structures' [4]. Simpler said, dualism allows mistaken beliefs about that patients themselves, or their bodies or surrounding social forces, are the sole determining factor for individual health. Persistent somatic symptoms go with problems of being as one thinks that one should be, wants to be, or once was [5].

Between October 2011 and May 2013 a computer game named 'LAKA' was developed by a Dutch rehabilitation centre, and planned to be offered during multidisciplinary rehabilitation to patients with chronic pain, fatigue, or musculoskeletal symptoms with high burdens of functioning. The idea that inspired the design of LAKA was to promote skills for dealing with 'existential' issues, including the question: "how do I want to live?" It was expected that such skills relate to key mechanisms of sustainable change in various health outcomes, including symptom severity, psychological distress, psychological well-being, and social participation. LAKA introduces forms of skill training in virtual social interactions, and encourages repeated skill practice and performance in the context of daily life. It was assumed that the contemporary modality of computer gaming might suit with varying or changing preferences of patients, and motivate skill training independently of care providers. This thesis evaluates these ideas, focusing on observing and explaining changes in patient outcomes after 'biopsychosocial' programmes by additional facilitation with a game like LAKA.

1.2 THE BIOPSYCHOSOCIAL MODEL

To oppose dualist and reductionist dogma in health care, Engel introduced the biopsychosocial model of health [6, 7]. This model adopted a kind of 'systems thinking' wherein biological processes are nested in, and interact with, psychological and social processes. An ideal biopsychosocial understanding of a patients' condition covers the patterns of interactions of inseparable biological, psychological and social processes. This became a preferred way of thinking about the managing persisting symptoms of pain, fatigue, and depression in patients with functional somatic syndromes (FSS) and chronic pain (CP) [6, 8, 9][1]. Across several of those conditions, including chronic low back pain, fibromyalgia, chronic fatigue syndrome, and tension headache, the existing evidence supports explanation by the mechanism of sensitization, or amplification of neural signalling, within the central nervous system [10]. In specific functional somatic syndromes, there may also be other biological abnormalities [8]. On a psychological level, certain dysfunctional ways of thinking about symptoms were identified, such as catastrophizing, hypervigilance, and fear avoidance beliefs, which result in a lesser moderation of pain signals in the central nervous system [11]. Accordingly, structural changes in the brain were found after cognitive behavioural therapy in patients with chronic pain conditions [12, 13].

Therefore, symptom patterns are potentially improved by 'bottom-up' approaches (targeting peripheral organic systems with pharmacotherapy) and 'top-down' approaches (targeting cortical brain systems with neuroscience education, cognitive behavioural therapy, and exercise). Biopsychosocial management includes recommended steps of conservative unimodal pharmacological, psychological, or exercise-based treatments. But also multimodal treatments for improving physical and emotional functioning and minimizing iatrogenic harm due to incompatible beliefs between patients and care providers, like: "there must be a pure physical source" versus "symptoms only exists in the mind or brain" [8].

[1] The research for this dissertation concerns this population, which is described in more detail in later chapters.

1.3 General research gaps for understanding biopsychosocial treatment effectiveness

There are many challenges for research in providing evidence about the effectiveness of biopsychosocial interventions in patients with high burdens of persistent somatic symptoms. A key issue is that current evidence supports only modest effectiveness of biopsychosocial management options as compared with simpler ones [14, 15]. It is often not clear how and why certain treatments work to certain degrees across biological, psychological, and social levels, for which patients, and under what circumstances. For psychological treatments, it is not precisely clear what approaches (e.g. “second” or “third wave” behavioural therapies), change techniques (e.g., problem solving, cognitive restructuring, etc.), and delivery modes (e.g., face-to-face or over the internet with certain levels of professional support) work best to improve outcomes in which particular patients in what particular circumstances [16-20].

Furthermore, there is concern about limitations to the methodological quality of previous effectiveness evaluations. Methods for blinding subjects to trial conditions are generally impractical whilst there has been a strong reliance on patient self-reported symptoms in the absence of practical and agreed upon measures of physical performance, participation in social roles, or biological changes [21-23]. This hinders empirical evidence of intervention effects across the different levels that constitute ‘biopsychosocial’ changes. Moreover, developments in methodology promise for improved capacity to evaluate interventions that, like most biopsychosocial treatments, consist of multiple components and are delivered in complex health care contexts: in patients with comorbidities, a history of previous treatments, by multidisciplinary teams, etc. [24, 25]. This promise corresponds with the current challenges.

Bridging explanatory gaps regarding what causes important health benefit, in what respect, for whom, and when, is important for enabling efficient use of scarce resources and keeping treatment options financially viable [9, 26, 27].

1.4 GAPS IN UNDERSTANDING THE EFFECTIVENESS OF BEHAVIOURAL CHANGE SUPPORT BY MEANS OF COMPUTER AND GAME-BASED INTERVENTIONS

Application of computer technology, such as websites, for offering behavioural change support, is typically motivated by benefits in costs, convenience and accessibility, and supplier control of the intervention [28, 29]. Serious games are a computer-based intervention that could offer the relative advantage of user enjoyment in addition to modest improvements in knowledge, behaviour, and clinical outcomes [30]. However, efficacious interventions require adequate implementation in real health care settings in order to be also effective [31]. Before large parts of the intended patients can use technologies for the provision of health services, challenges of adoption, abandonment, and scale-up are to be overcome [32]. A relevant problem of this kind was identified in trials of internet-delivered psychological therapies, in which participant attrition and non-compliance rates were higher than when similar treatments were delivered face-to-face [33]. In response to this problem, studies suggested that patient engagement with such technologies is enhanced by including the provision of personal advice and feedback, and by making sure that health issues addressed are perceived personally relevant [34]. Participative and persuasive design approaches may offer means to achieve this [35]. Moreover, 'blending' the qualities of computer technology and face-to-face contact was proposed, but it is yet to be discovered how this is done in best possible ways across different contexts [18]. These challenges may equally apply for patient use of serious games, and empirical work on this topic appeared only very recently [36, 37]. Thus, inherent entertainment qualities do not automatically imply successful implementation in the context of regular health care services, which matters for establishing effectiveness. LAKA and initial basic ideas about how and why it could work during rehabilitation are described in textbox 1.

Textbox 1: Early development and description of LAKA.

In early development stages, serious gaming design was mostly based on knowledge of experienced health care professionals, whose thinking about patients' health, wellbeing, and cognitive-behavioural change were, subsequently, interpreted as:

- 'positive' (health is seen as an ability to adapt and self-manage in the face of social, physical, and emotional challenges) [38];

- eudaemonist (health is importantly explained by finding purpose and meaning in life) [39], and;
- in accordance with a "3rd wave" or response-based approach to behavioural change [20, 40].

The intention is to encourage development of skilful response in functional contexts (that provide social and emotional rather than physical challenges). This is an approach to changing behaviours that can be distinguished from attempt to change specific supposedly dysfunctional antecedent cognitions. Instead, the goal is to stimulate adequate meta-cognitive processes of reflecting on one's own thought, emotion, and behaviour [20]. Herein, meditation (focused attention and open monitoring) practice was considered highly important for skill development and changing the experience of living with chronic pain [41].

Developers had specific ideas about motivating and enabling patients to practice these abstract adaptive skills. That is, by teaching about certain heuristics (a reference set of behavioural principles that are not too abstract, easy to conceive, and agreed with by most people): generosity, moral discipline, patience, enthusiastic perseverance and mental stability. These developer ideas inspired the design choices for the game-play.

Moreover, there were unspecified expectations that stronger immersion in skill trainings within game scenarios would improve engagement and effectiveness for complementary effects for part of the patients in rehabilitation. After LAKA was built, the design principles were framed as corresponding to a broad conception of 'mindfulness': one that includes a prosocial element similar to the heuristics applied in the design [42].

LAKA is an adventure game that is easy to control. It combines 2- and 3 dimensional visual environments, and has an emotionally rich comical style and immersive sounds. A player chooses a personal Avatar (male/female) to represent him/herself on a trip around the world. In an introductory storyline, the Avatar is depicted as someone in a deteriorated physical and socio-emotional state and who is determined to change his/her life. The Avatar meets the virtual teacher named Laka, who challenges the Avatar to make conscious choices in meetings with other people while travelling to 4 destinations: London, Turkey, Asia and Africa. At each of these destinations, the Avatar encounters 4 different scenarios in which he/she makes difficult choices in which responses from the environment can vary and are difficult to predict, for example due to unknown local customs and characters. At every moment there are 5 possibilities that, to varying degrees, demonstrate insight into "insightful" social responses. It is assumed that adequacy is characterized by "generosity", "moral discipline", "tolerance" and "enthusiastic perseverance" (for example, helping another person or adhering to set goals). Between these encounters, there is an opportunity for distraction in the form of a puzzle or driving a vehicle (mini-games) to get to the next location. A meeting with Laka follows at the end of each destination. He asks for a self-assessment of how it went, shares his own view of it, which also shows to what extent the Avatar and Laka agreed on the 'quality' of the choices made. During the journey to a next location, instruction is given for exercises, lasting 3 minutes, for improving focused attention and open awareness. After four destinations, there is a festive conclusion and the invitation to relive the journey differently in a second journey.

1.5 RESEARCH OBJECTIVES AND QUESTIONS

Firstly, performing a high quality assessment of the effectiveness of LAKA was considered scientifically relevant. Previous studies identified a general lack of powerful studies on whether video game technology could facilitate desirable individual health improvements [43, 44]. Another contribution aimed in this thesis is to understand the effectiveness of behavioural change support in biopsychosocial management, when offered by means of computer applications like the internet and serious gaming, in patients with complex chronic somatic health conditions. Application of computer technology can imply various changes in health care contexts, such as improving accessibility to patients who would otherwise not receive certain efficacious resources because of barriers like fear of being stigmatized or living too far away from a specialized clinic. Or, computer technology could provide a more efficient substitute of face-to-face delivery of similar content, or complement during or after biopsychosocial treatment in regular clinics for increased independent engagement without additional visits (doing more at home). Within this wider aim, the primary focus is on the effectiveness of complementing regular multidisciplinary rehabilitation with additional serious gaming. Therefore, it is questioned:

Research question 1: To what extent (in what respect and for how long) are computer-based behavioural change interventions effective for patients with complex chronic somatic symptoms? This question includes:

To what extent (and in what respect) is multidisciplinary rehabilitation with serious gaming effective as compared to multidisciplinary rehabilitation without serious gaming?

Secondly, the results of previous studies on computer-based interventions suggest uncertainty of eligible patients' perceptions about a serious game such as LAKA, which may determine their acceptance and actual use in the context of a rehabilitation programme [45]. Such information is needed by researchers and policy makers for determining if a serious gaming intervention could be deployed in a feasible way. That is: reaching a sizable group that represents the actual population of patients for studying effectiveness in the context of multidisciplinary rehabilitation, or – if proven effective – for implementing serious

gaming across different patients and health care contexts. For informing improvement, it is also useful to understand why it is more or less feasible for certain patients. Therefore, the question is:

Research question 2: Why and for whom is Serious gaming feasible, i.e. demanded (accepted and used) and implementable, as a complementary intervention during the multidisciplinary rehabilitation of patients with complex chronic somatic symptoms?

Third, recent developments in methodology are visible in refinements of Medical Research Council guidelines and growing popularity of realist evaluation approaches for evaluating health interventions under complexity [24, 46]. As stated before, these developments are promising for addressing current research gaps. Advancing methodological approaches provide improved starting points to question not only 'whether', 'to what extent', 'in what respect' and 'for how long', but also: 'how', 'why', 'for whom', and 'when' changes in treatment modes of delivery result in outcome changes. Thus, besides prove of validity in an average effects on learning and health outcomes at appropriate lengths of follow-up, explanatory insights can be gained regarding the thoughts, emotions and behaviours of patients that are being triggered by intervention resources in context. Moreover, one could identify characteristics of patients for whom mechanisms are triggered and outcomes change particularly weakly or strongly. Such insights can inform intervention decisions of design, selection, allocation, or tailoring (personalization of advice and feedback). Finally, it is useful to know about the kind of circumstances for patients (within settings) that enable or hinder the triggering of productive responses. Altogether, these may be the kinds of information that health care professionals and policy makers actually need most for developing, implementing, and providing computer-based interventions such that they are feasible and effective in different individual patients and local health care settings. Therefore, the final research question is:

Research question 3: How, why, for whom and when are computer-based behavioural change interventions effective in patients with complex chronic somatic symptoms? This includes:

How, why, for whom and when is multidisciplinary rehabilitation with additional serious gaming effective as compared to multidisciplinary rehabilitation without serious gaming?

1.6 OUTLINE OF THE THESIS

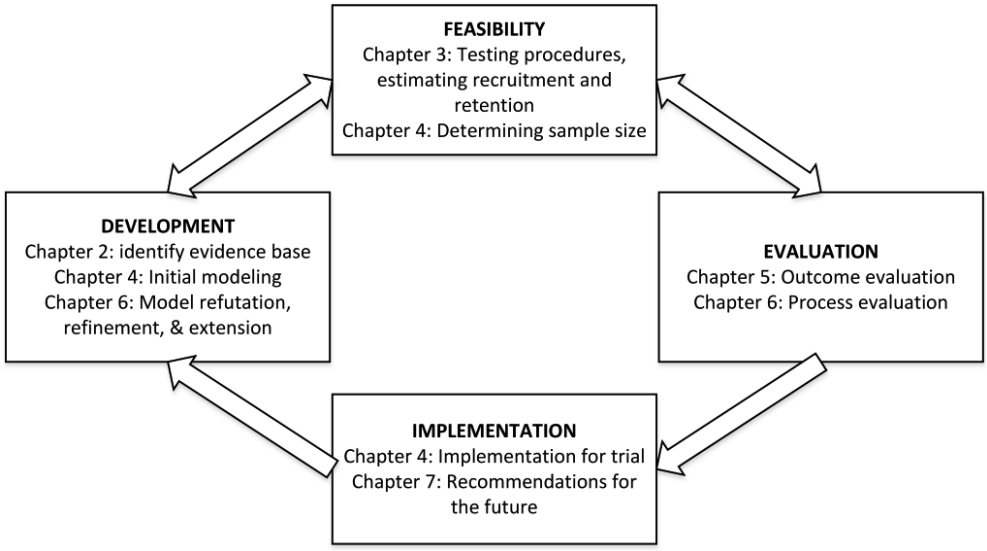
The set-up of evaluation procedures was informed by the Medical Research Council (MRC) guidelines for evaluating complex interventions [47, 48]. How the structure of the thesis relates to MRC guided procedures is depicted in Figure 1. In the following, it is explained how thesis chapters address the research questions.

Chapter 2 provides topical information for answering the first research question. For the evaluation trajectory of serious gaming, this chapter identifies the current evidence on the effectiveness of computer-based interventions in patients with CP or FSS, which largely share the characteristics of eligible patients for multidisciplinary rehabilitation. Hereto, a comprehensive systematic review and meta-analyses were performed on clinical studies that reported outcomes of computer-based interventions in comparison to control conditions. Meta-analyses were used to assess how strongly average outcomes differed between intervention groups that followed computer-based intervention and patients who were part of control groups. In addition, if study group outcome differences ('effects') varied substantively between studies, it was explored which reported characteristics of interventions, patients, and setting could distinguish between particularly weak and strong effects. This way of extracting, describing, and analysing these data also contributed with indications for responding to research question 3.

Chapter 3 commits to research question 2, and serves the evaluation process in preparing for subsequent full-scale evaluations of LAKA. The stage of development of LAKA at the start of the research warranted feasibility testing with the preparatory aims of (1) explaining variation in degrees of usage of LAKA as depending on perceptions and other differences between patients, and (2) providing a comprehensive feasibility description from patient users' perspectives. Because these aims are largely about informing study procedures and for success in participant recruitment and retention in the context of a subsequent evaluation, a pragmatic approach to mixed-methods was justified. A pilot

experiment was performed wherein LAKA was offered to eligible patients, via a web-site that provided access to download and installation instructions, for to be used under 'ad libitum' conditions. First, patterns were established between quantitative measures of patient characteristics, perceptions, acceptance (use intentions) and use of LAKA. Subsequently, explanations for quantitative data-patterns were obtained with qualitative data from semi-structured interviews with selected patients. Recommendations were given for future improvement.

Figure 1: Structure of the thesis in connection to the steps of evaluation



Adapted from Craig, et al.: Developing and evaluating complex interventions: the new Medical Research Council guidance [47]

In Chapter 4, a study protocol is described for full-scale outcome and process evaluations of serious gaming in addition to multidisciplinary rehabilitation. It describes the steps by which answers to the first and third research questions were obtained in the last two studies. The protocol builds on existing literature about relevant health outcomes and intermediate learning results of mindfulness-based and biopsychosocial intervention for intended patients, particular experiential qualities attributed to serious gaming for facilitating change, and implementation factors. Based upon this literature, designer assumptions were interpreted, and initial expectations were informed. Furthermore, the study method of an embedded quasi-experimental mixed-methods design are

described, including interventions and procedures as informed by feasibility study results, methods of data-collection, sample size calculation, and analyses.

Chapter 5 presents the results of outcome evaluations as described in chapter 4. These findings relate to research question 1. It primarily describes the difference in outcomes of pain intensity, fatigue, pain catastrophizing, and psychological distress between an experimental group of 156 patients who received an additional 'blended' serious gaming intervention during weeks 9-12 of a 16-week multidisciplinary rehabilitation programme with a group of 119 control group patients who followed the same programme without serious gaming at two similar sites of the same clinic. Multivariate linear mixed modelling was used for estimating a group difference in outcome changes over time between half-way the programme (just before serious gaming interventions started) and after the programme, taking the course of change from pre-treatment to half-way the treatment into account. Additional information is provided about the respects in which outcomes differed in time between groups, including qualitative data, implementation success in terms of patient adherence, and quantitative assessments of secondary outcomes: functioning, general health, impressions of change and satisfaction about the treatment.

Chapter 6 is dedicated to process evaluations for answering research question 3, also on the basis of the steps described in chapter 4. As the aim of this chapter is to provide answers in the form of a transferable 'programme theory', a realist approach to evaluations was adopted. This means that a theory is constructed about configurations (C) by what characteristics of intervention (I) in context (C) with introducing serious gaming intervention that trigger certain mechanisms (M) that produce changes in relevant outcomes (O) (ICMOCs). These ICMOCs concern health outcomes, as well as intermediate learning results and feasibility processes (i.e., perceptions of acceptance). Again, mixed methods are used, whereby additional qualitative and quantitative data were collected during the experiment (as described in chapter 5). Qualitative sources, including stakeholder focus groups and patient semi-structured interviews were analysed before outcome data inspection for proposing alterations to initial expectations (or programme theory) on how serious gaming would work in context. Subsequently, these propositions focused hypotheses formulation and testing by means of multiple

regression and (moderated) mediation analyses, which then again provided complementary indications for programme theory support, refutation, refinement, or extension.

Chapter 7 presents an overall discussion on the previous chapters. This includes an overall summary of findings and reflection upon them by each of the three main research questions, methodological considerations, directions for future research, implications and recommendations, and a final conclusion. The emphasis here is on reflection on the logical next step of implementing transferable insights on serious gaming on a larger scale.

2 LITERATURE REVIEW

This chapter was published on May 16 2018 in PLoS one, and is referenced to as:

Vugts, M. A., Joosen, M. C., van der Geer, J. E., Zedlitz, A. M., & Vrijhoef, H. J. (2018). The effectiveness of various computer-based interventions for patients with chronic pain or functional somatic syndromes: A systematic review and meta-analysis. PloS one, 13(5), e0196467.

Title: The effectiveness of various computer-based interventions for patients with chronic pain or functional somatic syndromes: A systematic review and meta-analysis

2.1 ABSTRACT

Background: Computer-based interventions target improvement of physical and emotional functioning in patients with chronic pain and functional somatic syndromes. However, it is unclear to what extent which interventions work and for whom.

Objective: This systematic review and meta-analysis (registered at PROSPERO, 2016: CRD42016050839) assesses efficacy relative to passive and active control conditions, and explores patient and intervention factors.

Methods: Controlled studies were identified from MEDLINE, EMBASE, PsychInfo, Web of Science, and Cochrane Library. Pooled standardized mean differences by comparison type, and somatic symptom, health-related quality of life, functional interference, catastrophizing, and depression outcomes were calculated at post-treatment and at 6 or more months follow-up. Risk of bias was assessed. Sub-group analyses were performed by patient and intervention characteristics when heterogeneous outcomes were observed.

Results: Maximally, 30 out of 46 eligible studies and 3,387 participants were included per meta-analysis. Mostly, internet-based cognitive behavioural therapies were identified. Significantly higher patient reported outcomes were found in comparisons with passive control groups (standardized mean differences ranged between -.41 and -.18), but not in comparisons with active control groups (*SMD*=-.26 - -.14). For some outcomes, significant heterogeneity related to patient and intervention characteristics.

Conclusions: To conclude, there is a minority of good quality evidence for small positive average effects of computer-based (cognitive) behaviour change interventions, similar to traditional modes. These effects may be sustainable. Indications were found as of which interventions work better or more consistently across outcomes for which patients. Future process analyses are recommended in the aim of better understanding individual chances of clinically relevant outcomes.

2.2 INTRODUCTION

Computer-based interventions (CBIs) may be a particularly accessible means for improving health outcomes in patients with chronic pain (CP) or functional somatic syndromes (FSS) [49, 50]. CP is diagnosed in individuals seeking health care for pain symptoms that persist beyond a usual 3- to 6-month duration of organic recovery [9]. FSS are defined by functional disturbances and chronic somatic symptoms without a satisfactory explanation by organ pathology or disease [8]. The difference between CP and FSS is the "mandatory" presence of disturbing pain symptoms in CP that can accompany a disease (i.e., arthritis) and does not need to be present for the diagnosis of FSS (i.e., chronic fatigue syndrome, tinnitus). However, there is a vast overlap between CP and FSS. Both conditions cover a variety of bodily symptoms and involve organic systems, and several diagnoses fall under both definitions (i.e., fibromyalgia, chronic low back pain, and irritable bowel syndrome [IBS]) [8, 51]. Furthermore, evidence supports bio-psychosocial management strategies based on a stepped-care approach for both CP and FSS [8, 52]. Efficacious interventions for reducing experienced symptoms and functional interference, in order of increasing intensity, include conservative medical treatment, physical therapy, psychotherapy, or multidisciplinary rehabilitation in primary or specialized care settings [8, 52, 53]. Herein, CBIs could offer independent patient access to stand-alone programmes or complementary elements for further-reaching, stronger, or more enduring effects by increasing independent engagement and/or preventing relapse [54, 55].

Research and development of CBIs is motivated by the large burden of these disorders that are due to a high prevalence (e.g., 20–30% for CP [56, 57], 1–3% for chronic fatigue syndrome [58], and 10–15% for tinnitus [59]), co-morbid psychological distress, loss of productivity, absence of strongly effective medical treatment, and limited access to specialized health care [8, 9, 57]. CBIs may involve the use of the Internet [60], interactive voice response [55], mobile/smart phone applications [61], CD-ROM/DVD, or handheld computers as a delivery route [62].

2.2.1 Literature overview

Previous systematic reviews and meta-analyses investigated the impact of CBIs across populations with chronic disease or mental health problems, including CP and FSS conditions [49, 50, 60, 63-78]. Internet-delivered cognitive behavioural

therapy (CBT) is effective compared to waiting-list or usual care conditions and may be equivalent to traditional (face-to-face) delivery formats [60, 64, 79]. This was suggested for CP patients specifically in a systematic review and meta-analysis by Buhrman et al. [49] that included 22 randomized controlled trials (RCTs) (five were published by the first author). Applied Internet-based CBT programmes were described in narratives and modest effect size estimates were found for patients' reported pain intensity (Hedges' g=-.33), functional interference or disability (g=-.39), catastrophizing (g=-.49), and depression (g=-.26), which replicated earlier meta-analytic findings [60]. A study on the impact of self-help modalities (including CBIs) in patients with IBS found medium sized effects on somatic symptoms (standardized mean difference [*SMD*]=-.72), and a large effect on quality of life (*SMD*=-.84) that did not differ between computer-based or face-to-face formats [72]. Conclusions on the internal and external validity of these findings were drawn with caution due to a limited amount of high-quality randomized clinical trials (RCTs). It was suggested that future studies should focus more on methodological uniformity and quality, outcomes at long-term follow-up, direct one-to-one comparisons with various active treatments, and/or extended variety in participants and treatment settings [64, 69, 71].

Furthermore, there are knowledge gaps with regard to what works for whom, and when [79-85]. It remains unclear if CBI effects vary by intervention, patient (e.g., demographics), and context factors (e.g., the degree to which e-health trials resemble routine applications) [60, 61, 86, 87]. To meet the presumed potential of CBIs, developers and (clinical and policy) decision makers yet require knowledge about which CBIs will be effective for which patients with CP or FSS in actual health care settings [73, 88, 89]. Process analyses embedded in clinical trials can offer the best evidence on these matters and can be complemented with meta-analytic tests [85, 90]. Statistically significant moderators of outcome improvement were found in CP patients after Internet-delivered CBT in comparison with controls, but there was no consistent moderating factor across outcome domains [84]. Several studies suggested similar degrees of CBI effectiveness across sub-populations, but participant (self) selection could have restricted the observed amount of patient variation [80, 81, 83, 84]. Two meta-analyses, comprising a diversity of self-management interventions and patients with musculoskeletal pain, explored moderators of programme effectiveness [79, 82]. One found that professional guidance and

psychological components were associated with better outcomes [79]. The other one showed stronger effects in older participants but guarded against definite conclusions based on a limited amount of data [82].

2.2.2 Objectives

In order to aid decision makers in choosing the appropriate intervention strategy for specific populations and individuals, and to aid CBI developers in constructing effective interventions, the objectives of this meta-analysis were to establish the efficacy of CBIs and to elucidate patient and intervention characteristics. In light of ongoing accumulation of empirical data and the possibility of pooling the results from CBI effect studies for the largely homogeneous conditions of CP and FSS, the questions of this study where thus: (1) To what extent do CBIs result in better health outcomes after treatment and at follow-up experienced by patients with CP or FSS as compared to passive control conditions (i.e., waiting-list, usual or standard care, discussion boards, or standard patient information) and active treatment conditions?; (2) What are the characteristics of patients for whom computer-based interventions are most and least effective?; and (3) What are the characteristics of the most and least effective computer-based interventions? Based on existing evidence about CBIs, general positive effects, but no specific moderating patient or intervention factors were expected.

These objectives include consideration of the strength of evidence that depends on methodological threats to internal and external validity [91]. Important health outcomes for CP and FSS are patient-reported somatic symptom intensity, health related quality of life (HRQOL), functional interference (or disability, handicap, impact, or disturbance of activities due to somatic symptoms), catastrophizing (or acceptance, self-efficacy, or any other targeted cognitive process of outcome improvement) [92], and depression (as a commonly reported aspect of emotional distress) [78].

2.3 METHODS

The Cochrane Handbook of systematic reviews of interventions [90] was used to prepare the study protocol which was preregistered at PROSPERO (2016:CRD42016050839). Reporting was then guided by the PRISMA statement [93].

2.3.1 Inclusion and exclusion criteria

Study inclusion and exclusion were based on: patient (P), intervention (I), comparison (C), outcome (O), and study type (S) criteria (PICOS) [93]. Eligible studies focused on adult participants (17–67 years of age) with a CP or a FSS condition. CP or FSS was identified through case-finding (with valid diagnostic instruments) or clinician assessment (either during the study or before, as a basis for self-reference). This included somatic symptom disorders and medically unexplained physical symptoms (MUPS). Eligible studies investigated a computer-based intervention; in comparison with one or more control conditions of any kind (passive or active); for its effects on relevant health outcomes; in a RCT, quasi-experiment, or mixed-method study. Measurements were taken at baseline and post-intervention and/or at follow-up. CBIs are defined as programmes that require patient contributions by using a computer platform for direct access to personally relevant information and support in behavioural change and/or decision-making for health issues [94].

Studies were excluded: (1) if patient eligibility focused specifically on paediatric or geriatric populations, factitious disorders, a specific organic disease (e.g., migraine, multiple sclerosis, osteoarthritis) or psychiatric illness as a complication thereof, hypochondriasis [95], or individuals who did not report chronic somatic symptoms (e.g., individuals at risk targeted in primary prevention); (2) if experimental programmes were not CBIs (e.g., if a programme did not target patients themselves, was designed to be used exclusively with professional assistance, regarded participants as passive recipients, or only provided a means for distant communication with care providers); (3) if outcomes other than relevant health outcomes were prioritized (i.e., feasibility or technology acceptance), or narrow focus on somatic symptom outcomes (the only type of outcome reported); and (4) if study types were non-empirical, fully qualitative, uncontrolled, or not published as a full-bodied article in a peer-reviewed scientific journal.

2.3.2 Search strategy

On June 16th and July 1st, 2016, MEDLINE, EMBASE, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were searched for relevant studies published since January 1990 without language constraints. Search terms relating to the patient populations [96, 97], computer-based and

behavioural interventions [94, 98], and study types [94] from previously published Cochrane reviews were listed using the Boolean operator 'or' and combined using the Boolean operator 'and'. The search string was adapted for usage across bibliographic databases with available interfaces. The full search strategy for EMBASE is added in S1 Appendix, table 1.1. As additional methods to obtain an exhaustive set of peer-reviewed and published journal articles, references of previous systematic reviews and meta-analyses on related topics were checked [49, 50, 60, 63-66, 68-74, 76, 77, 79, 99-102], and backward and forward citations of eligible studies were checked in Web of Science [103]. Grey literature was not searched.

2.3.3 Study selection

A two-step selection protocol had been piloted, used, and refined. First, potentially eligible studies were identified by titles and/or abstract screenings. Two authors (MV and HV or MJ) independently screened half of the studies. After comparison, discussions revealed that none of the authors had excluded potentially eligible articles. Thus, MV screened the remaining half. Second, MV and MJ independently assessed the final full-text assessment of all potentially eligible titles, and discrepancies were resolved by discussions involving HV. Each study with relevant outcome data was eligible for meta-analysis.

2.3.4 Data extraction and management

A data-extraction form was composed, piloted, and discussed *a priori*. General and patient items were extracted by MV and checked by AZ. Relevant items for generalizability to routine applications according to the CONSORT statement for E-health [91] were among these general items: year of publication, setting (by continent), type of control group, methods of recruitment ("open" or "closed" population, participant screening methods), participant compensation, type of human involvement, and use of prompts/reminders. Patient items were (baseline) average age, proportion of females, the duration of symptoms, education level (proportion that completed tertiary education), employment, sick leave, depression, and somatic symptom intensity.

Intervention duration, compliance, and characteristics were independently extracted by MV and JG. Disagreements were resolved after discussion with AZ. Theoretical basis, mode of delivery and behaviour change techniques (BCTs) were

classified based on intervention descriptions using the uniform taxonomies from Webb et al. [17]. Accordingly, the 11 items on use of theory were clustered into three categories: referencing to underpinning theory, targeting of relevant theoretical constructs, and selecting recipients or tailoring interventions. The 11 items on mode of delivery were clustered into automated functions, communicative functions, and supplementary modes. For classifying BCTs, we used the updated Behaviour Change Technique Taxonomy version 1 (BCTTv1) [70, 104]. This is a hierarchically structured taxonomy of 93 distinct techniques that are grouped into 16 categories such as “goals and planning” and “social support”. Both coders were trained in the accurate application of the BCTTv1.

Two authors (MV and JG) extracted and double-checked all outcome information, including the administered self-assessment instruments, means, standard deviations, and sample-sizes for two “time points”: post-treatment and/or 6 months or more at follow-up. If multiple measures were available for the same outcome category, the following measures were preferred: visual analogue or numerical rating scales of pain intensity (current) for somatic symptom intensity, HRQOL total scores (general subjective health or mental health composite subscales if totals were not reported), (pain) interference for functional interference (otherwise disability, handicap, or disease impact), and catastrophizing (or acceptance/self-efficacy). Standard errors were converted into standard deviations. Baseline values were imputed for missing standard deviations for outcomes post-treatment or at follow-up (i.e., if only change scores were reported).

2.3.5 Risk of bias rating

Quality assessment of the studies was performed by MV and JG based on the 13 risks of bias criteria recommended by the Cochrane Collaboration Back Review group [105]. Discussions with HV enhanced the objectivity and consistency of this assessment. The columns of S1 Appendix, table 1.2, detail the 13 criteria. Subsequently, the 13 criteria were combined into seven major categories of the general Cochrane risk of bias tool: selection bias, attrition bias, reporting bias, performance bias, incomplete data extraction bias, detection bias, and other risks [106]. Methodological limitations that pose a general threat for this type of intervention studies (lack of blinding) were ruled out in this categorization. A category was scored “high risk” if high risk was scored for one or more underlying

criteria, assuming that a single source of risk could bias the results of a trial completely [107]. “Low risk” was scored if all underlying criteria were “low risk.”

2.3.6 Determining the efficacy of computer-based interventions

To estimate CBI outcome levels against controls, pooled effect sizes were calculated by using the Review Manager Software package (RevMan 5.3) [90, 108]. Comparisons were categorized as CBI versus passive controls (e.g., “waiting-list”, “usual/standard care”); or CBI versus active controls (e.g., same content in face-to-face format). Outcome data were inserted such that negative numbers represented lessening of symptoms and overall that lower numbers represent more favourable outcomes for intervention group participants. If a comparison had to be chosen from multiple relevant options within a study (with multiple CBIs), the newest and/or most elaborate CBIs (i.e., “third-wave” CBT, or with more BCTs and/or delivery modes) were designated as experimental, while the simplest and most traditional interventions were chosen as controls. Twenty primary meta-analyses were performed for the two comparison types and five outcome categories by the two time-points.

For each meta-analysis, RevMan operations were set for inverse variance methods of estimating random effects on the basis of standardized differences between intervention and control group means (*SMD*s), anticipating on heterogeneous estimates in continuous outcomes and the use of different questionnaire instruments across studies. Chi-squared tests indicated if there was significant heterogeneity of *SMD*s across studies (cut-point: $p<.05$), and the I^2 statistic indicated the extent to which heterogeneity affected the pooled result. Applicable thresholds for (rough) interpretations of I^2, with 0% to 40% as potentially unimportant, 30% to 60% as modest, 50% to 90% as substantial and 75% to 100% as considerable heterogeneity were conservatively applied [45]. Funnel-plots were visually inspected for indications of publication bias. Further analyses, by calculating *SMDs*, on risk of bias sensitivity were performed only for studies that were assessed low risk of bias for each category. Hereto, it was also checked if study level sources of risk were similar on the outcome level (i.e., if unbalanced baseline group scores were a risk for a particular outcome). Similar sensitivity analyses were conducted based on source of recruitment (“open” versus “closed”) to explore effects by differences in health care settings [91].

2.3.7 Determining patient and intervention characteristics of effective computer-based interventions

Per meta-analysis with statistically significant and "potentially important" heterogeneity, two sub-sets of studies were created: one for the 25% highest study group differences (*SMD*s) and one for the 25% lowest *SMD*s. Within each set, patient and intervention characteristics (potential effect modifiers) were described by a summery statistic (count, proportion, or mean). To reduce the number of plausible sub-group analyses, characteristics were deemed 'distinctive' and tested (χ^2) if they differed substantially between the two sets, and/or from expected values (within sets of all studies or comparison types). Analyses were only conducted if 10 or more studies were available for analysis [90]. Study level associations (Chi-square tests, Kendall's Tau, or Pearson correlations) were calculated between intervention and patient factors to examine potential confounding of modifiers (using SPSS 22).

2.4 RESULTS

2.4.1 Search

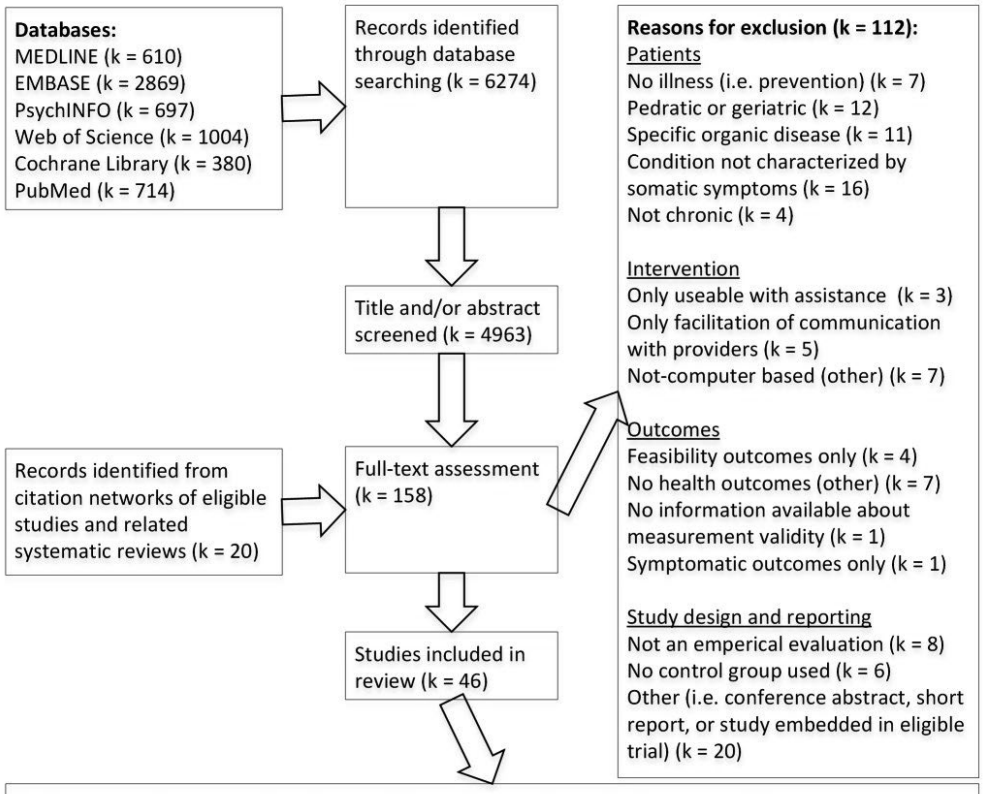
Search and study selection procedures are summarized in the PRISMA flow-diagram (Figure 1). In total, 4,963 unique hits were identified from the databases. Twenty additional studies were found in the citation networks of eligible studies or references of systematic reviews or meta-analyses on related topics. After tentative steps of title and abstract screening, 158 studies remained, nine of which were short reports or conference abstracts. Therefore, 149 full-bodied peer-reviewed articles were assessed full-text on the alleged inclusion and exclusion criteria. The final set consisted of 46 eligible studies (k) [29, 55, 62, 109-151].

2.4.2 Study characteristics

Over time an increase in eligible publications was found. Whereas in the period 2000-2007 only zero to one article per year had been published, this number rose to six to seven per year in the years 2013-2015. Of the included studies, only one study was not an RCT. Thirty-seven studies compared a CBI with a passive control condition (waiting-list, k=14, usual or standard care, k=9, message/discussion board, k=8, provision of information, k=6), whilst 16 studies compared a CBI with an active control condition (a simpler version of the same CBI, k=9, active

treatment without the additional CBI, k=3, or face-to-face CBT group, k=4). Six studies had multiple arms including comparisons with passive as well as active conditions.

Figure 1. PRISMA flow-diagram of studies.



Studies and participants included in calculations of (pooled) standardized mean differences:

Outcome	1. CBI versus passive controls (k=35)		2. CBI versus active controls (k=15)	
	Post	Follow-up	Post	Follow-up
Somatic symptoms	1.1 k = 29, n = 3284	1.6 k = 4, n = 1015	2.1 k = 11, n = 1292	2.6 k = 5, n = 683
Quality of life	1.2 k = 14, n = 1408	1.7 k = 1, n = 651	2.2 k = 6, n = 761	2.7 k = 3, n = 461
Iinterference	1.3 k = 30, n = 3387	1.8 k = 4, n = 1015	2.3 k = 10, n = 1097	2.8 k = 6, n = 672
Catastrophizing	1.4 k = 24, n = 2900	1.9 k = 4, n = 1015	2.4 k = 10, n = 946	2.9 k = 5, n = 432
Depression	1.5 k = 24, n = 2221	1.10 k = 4, n = 416	2.5 k = 8, n = 646	2.10 k = 6, n = 517

k: number of studies, n: number of study participants, OC: outcome, SS: Somatic Symptoms, HRQOL: Health Related Quality Of Life, FI: Functional Interference, CAT: Catastrophizing, DEP: Depression.

Three studies (two passive and one active comparisons) did not contain sufficient information for extracting means and standard deviations. Twenty-nine studies

were based in Europe, 13 in the US, three in Australia, and one in Asia. In 28 studies, participants were recruited from a general "open" population (e.g., web-site enrolment) and screened for eligibility using web-forms (k=13), additional telephone interviews (k=8), or face-to-face interviews (k=6). Seventeen studies recruited exclusively from "closed" clinical or work settings. Seven studies recruited from open as well as closed populations, and one did not report recruitment source. Most studies explicitly selected participants with the ability to use the required computer technology, including the Internet (k=32), touch key telephone (k=1), or smartphone (k=1). More implicit selection procedures were present in 12 studies, of which three studies used a run-in period. In six studies, monetary compensation was provided for study participation. About 60% of the included subjects completed the interventions (proportion on average was .59, *SD*=.23, range=.21-1, k=31). S1 Appendix, table 1.3, contains an overview of the questionnaire instruments for which data were extracted across outcome categories.

2.4.2.1 Participants

Patient conditions targeted by CBIs were mixed chronic pain (k=15), chronic (low) back pain (k=6), chronic widespread pain/fibromyalgia (k=6), mixed or tension headache (k=3), IBS (k=7), chronic fatigue (k=1), interstitial cystitis (k=1), non-cardiac chest pain (k=1), and tinnitus (k=6). Participants were on average 45.4 years of age (*SD*=5.2, k=44). Average proportions of patient characteristics showed that 71% of the participants were female (*SD*=.22, k=45), 42% had completed tertiary education (*SD*=.16, k=25), 67% were employed (*SD*= .19, k=21), and 36% were on sick leave (*SD*=.27, k=15). Somatic symptoms prior to treatment were reported for a mean duration of 115 months (*SD*=31, k=26), and studies that reported HADS depression at baseline (k=14) generally found no indication of depressive disorders (mean=6.7, *SD*=1.3).

2.4.2.2 Intervention characteristics

Experimental CBIs had an average duration of 10.5 weeks (range=3–52, *SD*=8.9) and were mostly (k=30) guided by one or more health professionals (mode=1, median=3, range=1–16; master's level psychologists, k=12; clinically trained, k=14). Most studies made use of prompts or reminders (k=31) that were sent occasionally depending on compliance (k=21) and/or scheduled automatically

(k=13). Behaviours mostly targeted by CBIs included exercise, sleep hygiene, relaxation, and leisure activities.

2.4.2.3 Theoretical basis and use of theory

S1 Appendix, table 1.4, presents the complete coding results for use of theory (1). To summarize, CBT approaches prevailed (k=33) across the studies that mentioned or referred to a theory about relationships among relevant concepts (item 1, k=39). Sixteen studies explicitly described their approach as CBT. Seven studies specifically mentioned third-wave CBT approaches, including Acceptance and Commitment Therapy (ACT) and mindfulness-based therapies. Others mentioned a combination of CBT with third-wave (k=6) or other conceptualizations (k=4). The remaining studies either referred to the empowerment model (k=3) or a model constructed by the author (k=3). Targeted constructs from the theory were mentioned as a predictor of behaviour (k=11) and/or for selection of intervention techniques (k=21). Theory or predictors were rarely used to select recipients for the intervention (k=1) or tailor the intervention to recipients (k=1). Explicit descriptions of links between techniques and relevant constructs were identified in 19 studies.

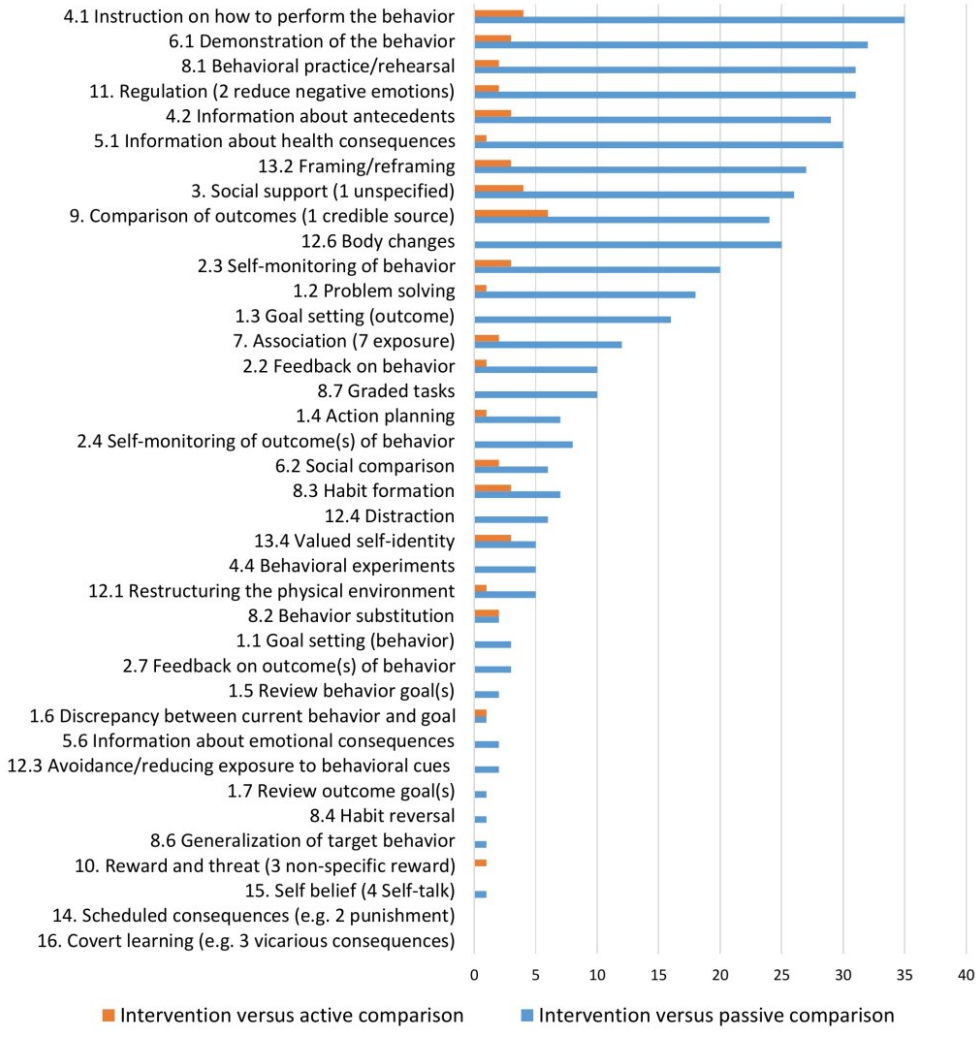
2.4.2.4 Behavioural change techniques

Figure 2 summarizes for how many studies certain BCTs were coded by each comparison. S1 Appendix, table 1.4 (2), fully describes the study and comparison level coding results after listing the precise interpretations of the coders of the 93 BCTs across the 16 categories.

Techniques implied by the description of 'relaxation' or 'meditation' were coded most often (k=31-37). Those techniques included the codes of performance instructions (BCT code 4.1), demonstration (6.1), prompting practice and rehearsal (8.1), and reduction of negative emotions (11.2). Therefore, these were the most prevalently coded BCTs. Body changes (12.6) was coded as implied by the description of relaxation (k=25), but not of meditation. Intervention descriptions often mentioned that change support was delivered by trained professionals over the internet (k=27). Herein the BCTs unspecified social support (3.1) and credible source (9.1) were coded. When CBT approaches were described along with a specification of a treatment rationale that induced coding 4.2 and 5.1; clarifying relationships of behaviours with antecedents and their health

consequences. Descriptions of cognitive restructuring or defusion led to coding 13.2; the framing or re-framing perspectives on behaviour to change cognitions or emotions about it. Other regularly coded techniques (k >= 10) were self-monitoring of behaviour (2.4), problem solving (1.2), outcome goal setting (1.3), exposure (7.7), and setting and performing graded tasks (8.7).

Figure. 2. Numbers of studies in which Behavioural Change Techniques were identified by comparison

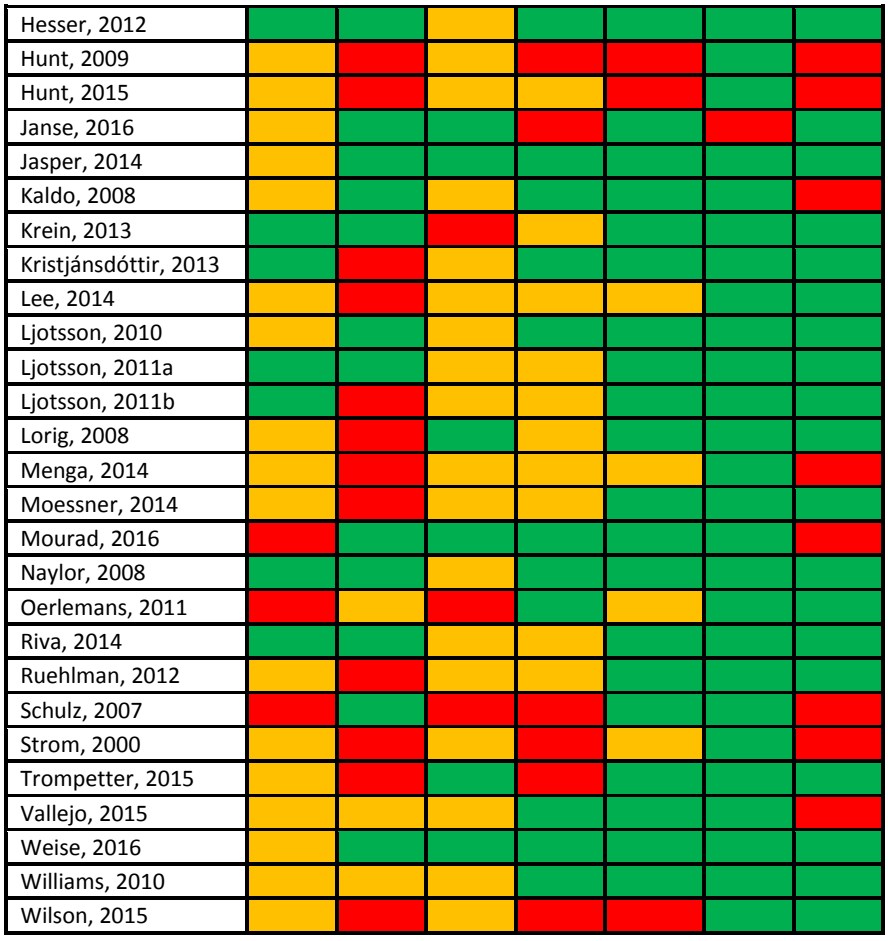


2.4.2.5 Mode of delivery

S1 Appendix, table 1.4, also contains complete coding results for use of theory (3). It shows that studies described various automated functions of their CBIs, including tailored feedback based on individual progress monitoring (k=37, 76.1%), an enriched information environment (k=25, 52.2%), and/or automated follow-up messages (k=32, 67.4%). Less often, interventions descriptions mentioned (two-way) communicative functions, such as communicating with an advisor through scheduled contact (k=24), access to an advisor for advice (k=4), and/or peer-to-peer access (k=11). Most studies mentioned the Internet (k=41), followed by e-mail (k=31), telephone (k=12), and SMS (k=7) as supplementary modes.

Table 1: Risk of bias assessment by 7 categories of the Cochrane Risk of Bias tool

First author, year of publication	Selection bias	Attrition bias	Reporting bias	Performance bias	Incomplete analysis according to group	Detection bias	Other bias
Abbott, 2009							
Andersson, 2002							
Andersson, 2003							
Boer, de, 2014							
Brattberg, 2006							
Buhrman, 2004							
Buhrman, 2011							
Buhrman, 2013a							
Buhrman, 2013b							
Buhrman, 2015							
Camerini, 2012							
Carpenter, 2012							
Chiauzzi, 2010							
Davis, 2013							
Dear, 2013							
Dear, 2015							
Devenini, 2005							
Dowd, 2015							
Everitt, 2013							



High risk is shaded red, unclear risk orange and low risk green

The 13 risk of bias criteria of the Cochrane Collaboration Back Review Group were combined into these 7 major categories of the general Cochrane risk of bias tool.

2.4.2.6 Risk of bias

As presented in table 1, none of the 46 studies were coded low risk of bias within all categories. Selection bias was coded low in 11 studies, meeting the three criteria of random sequence generation, concealment of allocations, and group similarity at baseline. Ten studies were assessed as low risk, while 25 studies were assessed as high risk of attrition bias. Thirty-four studies were classified as having an unclear risk of reporting bias through selective outcome reporting, because a study protocol was either not available or registered after the study was completed. For performance bias, 12 studies scored high risk and 18 studies low risk, which depended on differences in compliance and co-interventions between

groups. Only one study scored high risk for detection bias. Four studies were assessed as high risk of bias due to incomplete reporting and analysis according to group allocation, because findings differed between intention-to-treat and complete case analyses. This was unclear if no results of intention-to-treat analyses were reported (k=11). S1 Appendix, table 1.2, elaborates on the reasons authors agreed upon for assigning high, low, or uncertain risk by criteria.

2.4.3 Meta-analyses

Multiple meta-analyses were conducted for assessing the 20 direct effects of CBIs, which is too much for presenting each here in full detail. S1 Appendix, tables 1.5-.24, and figures. 1.1-1.29, contain full information on the direct effect estimates numbered per comparison, outcome type, and time of measurement. For each estimate, information is given on the *SMD* pooled for all eligible studies with its 95% confidence interval and heterogeneity statistics (I2, P-value). Furthermore, the same statistics are presented for sub-sets of studies with low risk across sources of bias, and for study sets that recruited patients from open or closed populations (sensitivity analyses). In addition, forest plots (providing detailed study level outcome information in a single overview) and funnel plots (visualizing study estimates relative to their sample sizes for detecting potential publication bias) are presented. Table 2 presents (per comparison, outcome type, and time of assessment) the pooled *SMD*s, appurtenant confidence intervals, and heterogeneity statistics and references to the 25% sub-sets of studies with highest and lowest *SMD*s. In the text, a factual summary is given, mentioning key information that is in S1 Appendix and not in table 2.

2.4.3.1 Computer-based interventions versus passive controls

After treatment, observed differences between CBI and control group means (*SMD*s) were significant and small- to medium-sized, ranging from -.18 for depression to -.41 for catastrophizing. For functional interference, somatic symptom intensity, and HRQOL heterogeneous estimates between studies were found (in the range for classification as 'modest' to 'substantial'), which could be further explored to its sources. Sub-group analyses of study sub-sets by risks of bias only showed significantly stronger (*SMD*=-.49 - -.53) functional interference outcomes after CBI versus controls in trials with low risk due to attrition (χ^2=7.97, p<.01) and performance (χ^2=5.10, p=.02). Inspection of funnel plots, most clearly

those for (post treatment) somatic symptom intensity and HRQOL, showed a lack of observations at the bottom-right corner (small studies with negative effect estimates) unlike the bottom-left corner (small studies with positive estimates).

At 6 or more months after treatment, small significant effect sizes (*SMD*=-.18 - - .32) were maintained for all outcomes except for HRQOL (k=1). There were too few studies available (1<k<6) for sensitivity analyses on follow-up results.

2.4.3.2 Computer-based interventions versus active controls

In comparisons of CBIs with active control groups, small positive significant outcome differences (*SMD*=-.15 - -.26) were only found for catastrophizing and functional interference outcomes after treatment. For both estimates, the between study heterogeneity estimate (I^2) was in the range of 'not important'. Within this comparison type, there were only enough data (k=10) to observe that the estimated effect on catastrophizing was significant and positive (*SMD*=-.33, 95% CI=-.49, -.17) within the sub-set of studies assessed with low risk of selection bias (k=5). At follow-up, no significant differences between CBI and active controls were observed (3<k<6, *SMD*=-.04 - -.031). Significant heterogeneity in the range of 'modest' or 'substantial' was observed for symptom intensity and HRQOL at both times of assessment, and for functional interference and depression at follow-up. Only for symptom intensity at post there were enough studies (k=11) for further exploration of sources of heterogeneity. For depression, heterogeneity was accompanied by an apparently outlying observation from a small study [148]. Further, researchers have not noticed anything unusual in the funnel plots of the smaller numbers of studies within this comparison.

Table 2: Overview of meta-analyses results for direct effects based on all eligible studies with relevant data

Outcome	**Effect size estimate**		**Heterogeneity**		**High 25% *SMD***	**Low 25% *SMD***
Study references	*SMD**	95% CI	I^2	P*	Study references	
CBI vs. passive controls						
Symptom intensity post[1] [29, 62, 109, 111-116, 118, 119, 122-124, 126, 128-130, 133, 135, 136, 139, 144, 146, 147, 150, 151]	-.35	-.48 - -.22	65%	<.01	[124, 128-130, 135-137]	[29, 109, 111, 115, 126, 144, 151]
HRQOL[1] *post* [29, 109, 112, 114-116, 126-129, 135-137, 139]	-.32	-.55 - -.10	70%	<.01	[128, 129, 137]	[109, 126, 135]
Functional interference post [29, 109, 111-116, 118, 119, 122-125, 127, 130, 131, 133, 135-137, 139, 140, 144, 146-151]	-.35	-.45 - -.25	45%	<.01	[29, 112, 114, 123, 127, 140, 149]	[109, 119, 135, 144, 146, 148, 151]
Catastrophizing post [29, 62, 113-116, 118, 119, 122, 123, 125, 127-129, 131, 133, 136, 137, 139, 144, 147-149, 151]	-.41	-.50 - -.31	28%	.1	n.a.*	NA
Depression post [29, 109, 111-116, 119, 122, 123, 125-127, 130, 131, 137, 142, 144, 146, 147, 149-151]	-.18	-.28 - -.07	29%	.1	NA	NA
Symptom intensity f-u[1] [119, 125, 139, 147]	-.18	-.30 - -.05	0%	.52	NA	NA
HRQOL f-u [139]	.13	-.02 - .28	/	/	NA	NA
Functional interference f-u [119, 125, 139, 147]	-.18	-.30 - -.06	0%	.62	NA	NA
Catastrophizing f-u [119, 125, 139, 147]	-.32	-.47 - -.17	19%	.30	NA	NA
Depression f-u [119, 125, 147, 152]	-.29	-.48 - -.10	0%	.59	NA	NA
CBI vs active controls						
Symptom intensity post [55, 110, 121, 122, 126, 132, 134, 138, 141, 143, 147]	-.16	-.35 - .02	56%	.01	[55, 147]	[134, 143]
HRQOL post [55, 121, 126, 127, 138, 141]	-.17	-.48 - .14	74%	<.01	[55]	[126]
Functional interference post [55, 110, 122, 127, 131, 132, 134, 141, 147, 148]	-.15	-.27 - -.03	0%	.7	NA	NA
Catastrophizing post [55, 110, 121, 122, 127, 131, 134, 138, 147, 148]	-.26	-.41 - -.10	21%	.25	NA	NA
Depression post [110, 127, 131, 132, 134, 138, 147, 148]	-.14	-.37 - .09	47%	.07	NA	NA
Symptom intensity f-u [131, 134, 138, 141, 147]	-.15	-.40 - .10	60%	.04	[138]	[141]

HRQOL f-u [127, 138, 141]	-.04	-.37 - .30	66%	.05	NA	NA
Functional interference f-u [127, 131, 134, 141, 147, 148]	-.20	-.44 - .05	56%	.05	[148]	[127]
Catastrophizing f-u [127, 131, 134, 138, 148]	-.27	-.56 - .02	53%	.08	NA	NA
Depression f-u [127, 131, 134, 138, 147, 148]	-.31	-.78 - .16	85%	<.01	[148]	[127]

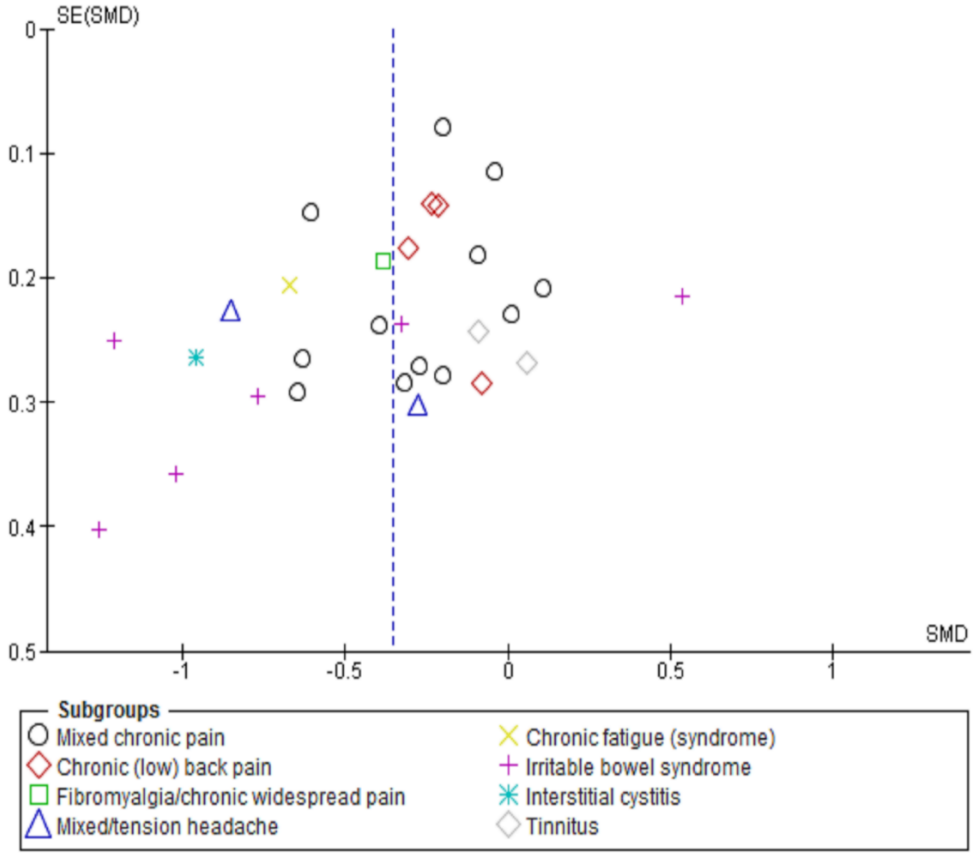
[1]*SMD*: Standardized Mean Difference; CI: Confidence interval; *P*: P-value for Chi^2 test of Tau^2 (heterogeneity); post: outcome measurement after treatment; HRQOL: Health-related Quality Of Life; NA: not applicable, because the degree of heterogeneity was statistically insignificant or unimportant, or because fewer than 4 studies reported outcome information in this category; f-u: measured at follow-up

2.4.3.3 Patient characteristics of effective computer-based interventions

S1 Appendix, table 1.25, presents results of the first (intermediate) step in exploring patient and intervention factors. Herein 6 table columns represent study sets: studies with passive and active comparison types and studies with the 25% highest and 25% lowest effect sizes (*SMD*s) within meta-analyses with sufficient studies (k=10) and significant heterogeneity (somatic symptoms at post and follow-up, and HRQOL and functional interference at post). Rows list control conditions and characteristics of patients and interventions. Cells contain corresponding statistics. S1 Appendix, table 1.26, completely presents the 42 sub-group analyses that were chosen to be conducted, along with their corresponding sub-group operationalization and test statistics (χ^2, *P*-value, and I^2). A full overview of associations between study characteristics is available upon the author's request. Here, significant findings are mentioned.

Between the 8 different sub-groups by patient conditions, different *SMD*s were seen for somatic symptoms after CBIs in comparison with passive controls (χ^2=15.62, p =.03). When comparing only the sub-group of IBS studies (k=6) with mixed CP studies (k=12) within the same meta-analysis, higher estimates are observed after also excluding one study on IBS patients with outlying (negative) results (k=17, χ^2=9.60, p<.01; Figure 3) [83]. For studies with a relatively lower average participant age (< 42.5 years), higher estimates were seen (at post) for somatic symptoms and HRQOL (χ^2=11.45 – 15.11, p<.01). Estimated effects on somatic symptoms (at post) were higher in study sub-groups with higher average proportions of female study participants (3 groups split by 2/3 and 4/5, k=29, $\chi^{2=}$9.19, p<.01), or with a higher proportion of participants with a completed tertiary education (2 groups split by 40%, k=17, χ^2=5.46, p=.02). Estimated CBI effects on functional interference (after treatment, versus passive controls) were higher for a subset of studies (k=4) with higher depression scores at baseline (Hospital Anxiety and Depression Scale >7) (k=11, χ^2=5.32, p=.02), and a subset (k=3) with more than 50% absenteeism among study participants (k=11, χ^2=3.73, p=.05). Finally, even without removal of a statistical outlier [83], estimates for a sub-group of studies (k=19) with explicit participant computer literacy selection criteria were lower than for studies (k=10) with unclear or implicit criteria (k=29, χ^2=4.79, p=.03).

Figure 3. Funnel plot for symptom severity scores post treatment by various patient conditions

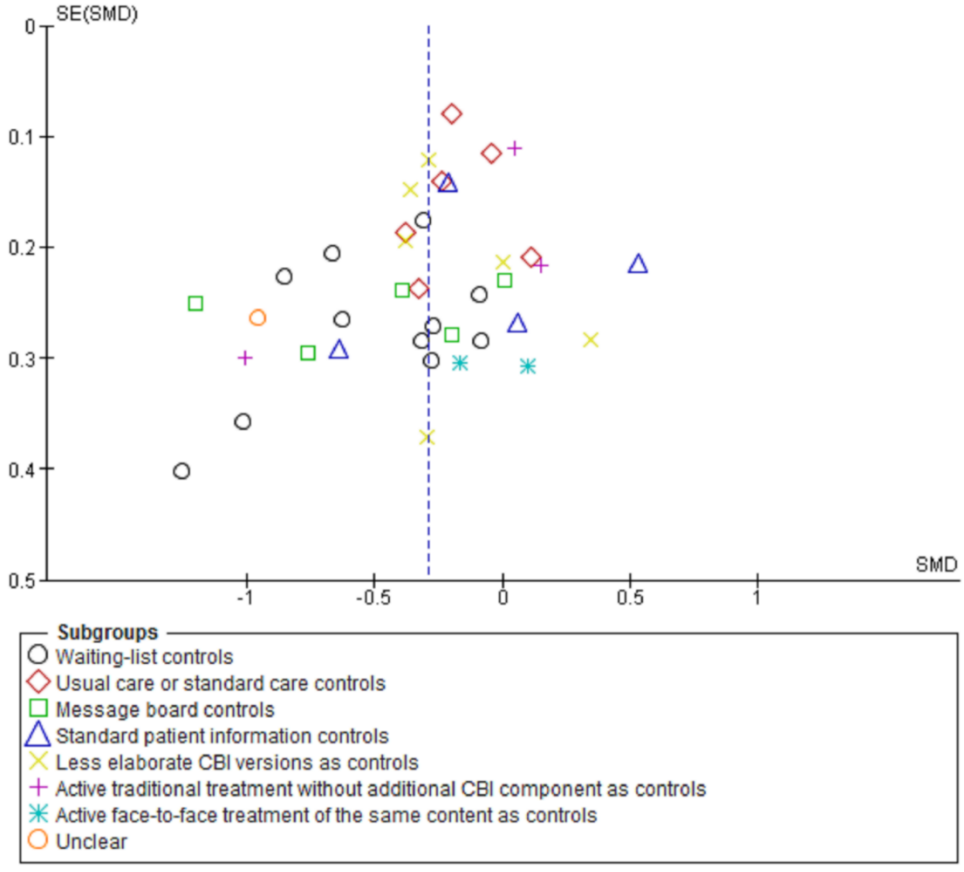


SE: Standard Error, SMD: Standardized Mean Difference.

2.4.3.4 Intervention characteristics of effective computer-based interventions

Efficacy estimates also varied by several sub-groups of intervention characteristics. Differences in *SMD*'s by the 4 types of passive control groups were found for somatic symptom, HRQOL, and functional interference outcomes at post treatment (χ^2=12.79 – 22.73, p =< .005). More specifically, efficacy estimates of studies on comparisons of CBIs with care as usual (*SMD*=-.04 - -.17) instead of waiting list controls (*SMD*=-.79 - -.43) were smaller (14<k<21, χ^2=10.78 - 11.06, p =< .001) (See Figure 4).

Figure 4. Funnel plot for symptom severity scores post treatment by various types of control groups



SE: Standard Error, SMD: Standardized Mean Difference. Comments: The meta-analysis presented here included the results for active comparisons (not the passive ones) from Trompetter et al. (2015) and Dear et al. (2015) to avoid double entries. Online discussion was facilitated for control group participants while being on a waiting list for receiving the experimental CBI.

Furthermore, differences of *SMD*s in functional interference outcomes were found by the presence of guidance or its levels of professionalism (k=30, χ^2=9.84, p=.02). Effects were generally small when guidance was absent (k=11, *SMD*=-.24), larger at master's level (k=7, *SMD*=-.38), and largest at clinical level (k=11, *SMD*=-.49; χ^2=9.84, p=.02). Post treatment *SMD*s in HRQOL for the sub-group of studies that reported the used of theory for the selection of intervention techniques (k=7, *SMD*=-.62) versus the studies that did not (k=7, *SMD*=-.08) were relatively higher (k=14, χ^2=5.79, p=0.02). For studies for which "exposure" (7.7) was coded versus

those for which it was not, *SMD*'s in (post-treatment) somatic symptom (*SMD*=-.67 versus -.26) and functional interference (SMD=-.50 versus -.28) were higher (χ^2=3.72 - 6.26, p =< .05).

For somatic symptom outcomes, it also appeared that higher *SMD*s between CBI and (both passive and active) controls were higher for sub-groups of studies that reported fewer (subsequently less than 5 or 2) rather than more modes of delivery (χ^2=5.11 - 6.34, p =<.04). *SMD*s in somatic symptom outcomes (at post) were higher (*SMD*=-.52 versus -.18) in studies reporting a 50% or higher CBI completion rate (k=20, χ^2=4.55, p=.03). Completion rate, on its turn, was associated with the use of occasional (instead of absent or scheduled) reminders (one-way ANOVA: F=3.06, p=.045).

2.5 DISCUSSION

2.5.1 Summary of evidence

This study questioned (1) the short and long-term efficacy of CBIs compared with passive and active controls for (self-reported) outcomes in patients with CP or FSS, as well as (2) patient and (3) intervention factors by which efficacy is high versus low. Generally, small effects were found when CBI was compared to passive controls. But when CBI was compared to active control groups, no significant differences in treatment effects were found. Small levels of efficacy were maintained for 6 months or longer. Strength of evidence varied by follow-up terms and type of comparison groups. Additionally, explorative analyses provided several (interdependent) possible patient and intervention characteristics that showed marked differences in treatment effects.

First, regarding efficacy, a small positive average effect of CBI is found in comparison with passive controls across all outcomes at post-treatment (i.e., somatic symptom intensity, HRQOL, functional interference, catastrophizing, and depression). CBIs predominantly included typical contents of CBT. This agrees with the up-to-medium sized effects observed in previous meta-analyses on the efficacy of Internet CBT in populations with CP [49, 60] and mental or chronic somatic symptoms at large [68, 77, 153, 154]. Additional meta-analytic evidence is presented (except for HRQOL) in support of the hypothesis that CBI efficacy is retained for 6 months or longer. This strengthens the previous suggestion that CBI effects would last at least up to three months [60]. Moreover, similar meta-

analytic results were previously found for depression [153]. Our meta-analyses do not suggest that CBIs have additional effects when complementing (during or after) face-to-face delivered multidisciplinary programmes (k=3), or when substituting traditional (group) formats of CBT (k=4). These findings concur with previous studies that suggested equivalence between computer- or group-based CBT across psychiatric and chronic somatic disorders [60, 64, 79]. In sum, CBIs offering complementary behavioural change content have, on average, small and prolonged effects on self-reported health in patients with CP or FSS.

Secondly, this study explored characteristics of patients with CP or FSS for whom CBIs are most and least effective. Different characteristics of patients included in studies were sometimes associated with significantly higher or lower CBI effects on somatic symptom, HRQOL, and functional interference outcomes. Even though effect estimates (i.e., for somatic symptom outcomes) could not be considered equal across different CP and FSS diagnoses, no particular diagnosis stood out. Unfortunately, the number of studies per diagnosis was too small to perform 1 on 1 comparisons between all diagnoses (all k<5 except IBS; k=6). For IBS, effect estimates were relatively high (medium sized), but one study had a deviating low effect, so that a difference with other diagnostic groups cannot be suggested on statistic grounds. This study by Everitt et al. (2013) differed from other IBS studies (but not from other included studies) by setting ("closed") patient factors (higher age and lower education level), intervention factors (lower compliance), and risk of bias criteria (low risk of reporting bias) [126]. It was also the only study that tested combinations of CBI and drug treatments that, according to the authors, could have affected patient expectations. Mechanisms of heterogeneous effects of IBS (self) management interventions have been largely unclear [81, 155]. Future research should clarify whether distinctive CBI efficacy has to do with differentiating characteristics of IBS, or other differences in interventions studied, patients, and/or context.

Exploration of other patient factors of CBI efficacy resulted in positive findings by demographics and health status. More favourable post-treatment somatic symptoms and HRQOL outcomes of CBI versus passive controls were observed for adult patient samples with a relatively lower (adult) age. Previous studies (process- and meta-analyses) of CBIs or self-help also found more favourable outcomes in relatively younger patients with chronic somatic or psychiatric conditions (for somatic symptoms and HRQOL [139, 156], and for functional

interference, cognition, and depression [82, 84, 85]). Thus, several powerful studies have now suggested (subtly) better effects of CBI in patients of relatively young adult age. Furthermore, this study found higher estimates of average CBI efficacy for somatic symptom intensity by higher proportions of females and highly educated patients, and for functional interference by initial depressed mood (mean HADS>7) and sick leave (> 50% of the sample). Higher efficacy estimates and proportions of highly educated patients came with absent reporting of explicit eligibility criteria for computer literacy. Authors of included trials expressed their uncertainty about whether outcomes were influenced by their methods of participant inclusion and could only refer to a single trial with depressed patients to contest this [131, 157]. Some previous studies also reported better HRQOL outcomes by gender [82], and better depression and/or functional interference outcomes by higher education, depression, and disability [80, 82, 84, 156]. In all, this and previous studies have been inconsistent about the significance, but consistent about the characteristics of CP or FSS patients for whom CBIs are more or less effective. This should not be seen as a reason to offer CBI only to certain patients, because effect sizes are significant for several outcomes in any sub-group. Rather, sensitivity to individual differences in responding may help to achieve the full potential of CBI in practice.

Third, explorations provided insight into characteristics by which CBI is most or least effective. Overall, this study shows that experimental CBIs were quite similar in terms of theoretical basis, behavioural change techniques, and delivery modes. Some aspects that varied between CBIs, including the use of theory for selecting intervention techniques, exposure techniques, and a limited amount of delivery modes were associated with relatively higher effects. Efficacy estimates in this study are relatively high for included studies that referred to third-wave CBT-models (Mindfulness and Acceptance Commitment Therapy) (i.e., for functional interference), but there was no statistically significant moderation effect by different theoretical (CBT) models mentioned. A previous study on the efficacy of face-to-face delivered third-wave therapies in CP suggested that it is a good alternative rather than superior to ‘‘traditional” CBT models [115]. This applies to CBI as well. Furthermore, efficacy estimates for functional interference increased with the presence and level of training of care providers. The importance of professional guidance was stressed before in reviews on CBI for health conditions and depression, and self-help for chronic back pain [34, 110,

116]. Efficacy in somatic symptom outcomes was raised by compliance, which appeared to increase with occasional reminders. Therefore, proficient guidance and compliance feedback may improve efficacy for some outcomes. No significant moderation was found by intervention duration, but efficacy seems highest in studies with a programme duration of 7 to 10 weeks. Previous meta-analyses were inconsistent in this regard [32, 34, 117]. It seems reasonable to expect that users need substantial time to process contents that are relevant to them and are likely to lose interest when a programme takes too long to complete [158]. Such differences would inform decision makers, clinicians, and developers about design qualities by which CBIs are comparatively efficacious or plausibly equivalent to active intervention through conventional means (face-to-face), i.e. if inaccessible or too costly.

2.5.2 Strengths and limitations

Study limitations were, first, that grey literature had not been searched and authors were not contacted for missing data. Thereby, a risk has been taken that relevant (negative) results are neglected. Secondly, moderator analyses were explorative and intended to inform hypotheses formulation. Since there were statistically significant associations between computer-literacy selection criteria, age, education level, IBS-diagnosis and reporting of 'exposure' techniques, it should be emphasized that subgroup analyses are not suitable for unravelling (spurious) relationships amongst (heterogeneous) outcomes and its factors. These exploratory analyses also overlooked sensitivity by risk of bias and did not enable to control factors for one another (as in meta-regression). Third, the performance of sensitivity analyses by extracted information about generalizability is not a well-established procedure. It is hindered by the novelty of reporting standards for E-health (since 2011) [91]. Because of understandable limitations in reporting at this time, authors agreed that converting reporting items (e.g., participant compensation, co-interventions, numbers and research engagement of providers) to classifications was too ambiguous. Nonetheless, this study has several particular strengths. An extensive search strategy was used, creating a good chance that found studies are exhaustive with regard to eligible full-bodied, peer-reviewed, and published articles. The pooling of outcomes for multiple “overlapping” adult patient conditions increased the number of included studies and meta-analytic power. Classification of intervention content with uniform and

empirically supported taxonomies was applied in a consistent, transparent, and independent way on the basis of intervention descriptions in study articles and research protocols [17, 104]. Finally, this is the first study in the field, by knowledge of the authors that included meta-analyses by independent assessment of risk of bias criteria, behavioural intervention content, and relevant items for generalizability.

It is due to these strengths that plenty of information is provided on outcome-level strengths and weaknesses. Regarding our first research question, strength of evidence for short-term CBI outcomes in comparison with passive controls is supported by the robustness of sensitivity analyses across most sources of bias risk. Nonetheless, studies of low risk of bias were minorities across criteria. Concerns for placebo effects also remain [159], because blinding of participants and staff are generally impractical, and different effect estimates were found by variety in control group interventions and their credibility as attentional placebos. Furthermore, inspected funnel plots did not fully contradict risk of reporting and/or publication bias. This was seen in a previous meta-analysis on self-help for MUPS, but not in meta-analyses on Internet CBT for CP [49, 159]. Therefore, explanations for funnel plot shapes could also be found in other methodological factors, such as the scale of CBI deployment (studies from the United States were typically larger scaled, less often professionally guided and reported relatively lower functional interference outcomes than European studies) [60, 68, 90]. Evidence for internal validity should be considered weak for longer follow-up terms or active comparison groups, because sensitivity analyses were undermined by the scarcity of high quality studies. Indications that a significant degree of effectiveness might be less certain when CBIs are offered to patients in closed clinical or work setting do not contribute to external validation (in routine deployment).

Regarding the second and third research question, important patient and/or intervention factors may be omitted that primary studies did not measure or measured by using different instruments (e.g., previous observations of better effects by higher levels of initial somatic symptoms and self-efficacy could not be replicated [81, 84, 156, 160]). In addition, the use of taxonomies for coding behavioural intervention content could only have led to valid data in so far as accurate descriptions were available. Moreover, findings on relationships between CBI content and outcomes are limited by lacking information about

fidelity, despite that standardized delivery is considered to be an important strength of CBI [150, 161, 162]. Overall, the evidence for patient and intervention factors of the heterogeneous efficiency of CBI in some outcomes remains weak.

2.5.3 Conclusions

In general there is a minority of decent quality information in support of a small positive average effect of CBI compared to passive control conditions on relevant (subjective) outcomes in patients with CP or FSS. There is weaker evidence that effects of CBIs last for 6 months or longer and similar to 'traditional' active treatment conditions. Evidence on CBIs complementary to active treatments are to scarce and diverse to draw conclusions. Therefore, the clinical relevance of CBI effects is generally limited for many individual patients with CP or FSS. Moreover, no certainty can be given that effects are generalizable to patients receiving CBIs in work or clinical settings.

Furthermore, there are indications that CBIs that facilitate compliance and "exposure" through specific delivery methods and expert guidance work best for relatively young, highly educated female patients with depressed mood choosing CBIs. However, which of these interdependent patient and intervention factors is decisive (and why) is not clear. More evidence is needed in support of indications that effects on other outcomes (symptom intensity, quality of life, and functional interference) can vary in consistency and strength, depending on whether interventions include theory-based change techniques, "behavioural exposure" specifically, or guidance by (schooled) professionals, or depending on whether (self-selecting) patients are younger, female, highly educated, absent from work, and/or experience more depressed mood. CBIs may not be more or less effective for emotional functioning (catastrophizing and depressed mood outcomes) with certain intervention or patient characteristics. More in-depth explanation is needed to better understand these factors across settings. On the basis of such information, clinicians and policy makers can improve decisions concerning CBIs in development, tailoring, quality assessment, and allocation to patients. Ideally, individual patients who are offered a CBI in regular patient care will get better chances of experiencing clinically relevant outcomes.

2.5.4 Future research

Ideally, the efforts of this study are continued by enrichment and refinement of the extracted data for updates. This could be done by collecting information first-hand from authors on intervention factors in compliance with the standard taxonomies and reporting guidelines. Tweaking the search string for improving balance between sensitivity and length would also be helpful. A network meta-analysis of the data could also provide more insight into the relative effectiveness of CBIs in relation to alternatives and each other. However, most progress may be achieved with additional primary studies and embedded process analyses. Future trials should focus on methodological quality, select common measurement instruments, investigate and report completely on selection processes during the recruitment stage, consider more information about patients related to self-selection (e.g., socio-economic status, self-efficacy in general or for using computers), include follow-up terms of at least 6 months, compare active interventions 1-on-1 (i.e., Internet CBT with vs. without exposure techniques), report intervention features and fidelity transparently and uniform. Finally, research should better explain under which conditions individual patients with CP or FSS have a better chance of achieving clinically relevant benefit from behavioural change through CBI than small average group effects imply.

Abbreviations:

- **BCT:** Behavioural change technique
- **CBI:** Computer-based intervention
- **CBT:** Cognitive behavioural therapy
- **CP:** Chronic pain
- **FSS:** Functional somatic syndrome
- **HRQOL:** Health related quality of life
- **IBS:** Irritable bowel syndrome
- **SMD:** Standardized mean difference

3 FEASIBILITY PILOT

This chapter is based on the following publication, published on April 1 2016 in JMIR Serious Games:

Vugts, M. A., Joosen, M. C., van Bergen, A. H., & Vrijhoef, H. J. (2016). Feasibility of applied gaming during interdisciplinary rehabilitation for patients with complex chronic pain and fatigue complaints: a mixed-methods study. JMIR serious games, 4(1).

Title: Feasibility of serious gaming during Multidisciplinary Rehabilitation for patients with complex chronic pain and fatigue complaints: a mixed-methods study

3.1 ABSTRACT

Background: Serious gaming holds potential as a convenient and engaging means for the delivery of behavioural interventions. For developing and evaluating feasible computer-based interventions, policy makers and designers rely on limited knowledge about what causes variation in usage.

Objective: This study looks closely at why and by whom a serious game (LAKA) is demanded, whether it is feasible (with respect to acceptability, demand, practicality, implementation, and efficacy) and a complementary intervention during a multidisciplinary rehabilitation programme for patients with complex chronic pain and fatigue complaints.

Methods: A mixed-methods design was used. Quantitative process analyses and assessments of feasibility were carried out with patients of a Dutch rehabilitation centre who had been receiving access to LAKA without professional support during a 16-week multidisciplinary outpatient programme. The quantitative data included records of routinely collected baseline variables (t0), additional surveys to measure technology acceptance before (t1) and after 8 weeks of access to LAKA (t2), and automatic log-files of usage behaviour (frequency, length, and progress). Subsequently, semi-structured interviews were held with purposively selected patients. Interview codes triangulated and illustrated explanations of usage, and supplemented quantitative findings on other feasibility domains.

Results: Of the 410 eligible patients who started an multidisciplinary rehabilitation programme during the study period, 116 patients participated in additional data-collections (108 with problematic fatigue and 47 with moderate or severe pain). Qualitative data verified that hedonic motivation was the most important factor for behavioural intentions to use LAKA ($P<.001$). Moreover, quotes illustrated a positive association between usage intentions (t1) and baseline level (t0) coping by active engagement (Spearman Rho=0.25, $P=.008$), and why patients who often respond by seeking social support were represented in a group of 71 patients who accessed the game ($P=.034$). The median behavioural intention to use LAKA was moderately positive and declined over time. Twenty patients played the game from start to finish. Behavioural change content was recognized and seen as

potentially helpful by interview respondents who exposed themselves to the content of LAKA.

Conclusions: Variation in the demand for serious gaming is generally explained by perceived enjoyment and effort, and individual differences in coping resources. A serious game can be offered as a feasible complementary intervention for more patients with complex chronic pain or fatigue complaints by embedding and delivery to align with patient experiences. Feasibility and (cost-) effectiveness can be evaluated in a full scaled evaluation. New observations elicit areas of further research on the usage of computer-based interventions.

3.2 INTRODUCTION

3.2.1 Background

Computer-based interventions (CBI) can be effective alternatives or complements to face-to-face delivery in psychological treatment and chronic illness management [60, 64, 163, 164]. However, systematic reviews on effectiveness of CBIs have been concluding that sizable and heterogeneous proportions of patients stop using CBIs before completion [165-167]. Non-usage attrition in CBI studies may depend on factors such as therapist involvement, demographics, computer self-efficacy, and health status [33, 166-170]. As a strategy to improve patient engagement, some CBI designs have incorporated interactive features [171, 172]. Interactive and visual enriched designs may support patient demand through perceived personal relevance, social support, and enjoyment [173, 174]. Accordingly, computer game technology has been serious to engage people and to promote health behaviours and clinical outcomes [30, 43].

Chronic pain and fatigue complaints constitute a major burden for individual sufferers and societies worldwide [8, 175, 176]. Functional Somatic Syndromes (FSS) are diagnosed by medical specialists when bodily functioning is disturbed, somatic symptoms persist longer than a normal healing process, and conditions cannot be fully attributed to a known conventional disease [177]. A high degree of commonality exists between FSS, wherein central sensitization may be a biological substantiation [178]. FSS can be precipitated by profound life events and cultural factors, and maintained by psychosocial factors [20]. Evidence has been supporting the effectiveness of various (cognitive) behavioural interventions in primary care settings, or within multidisciplinary rehabilitation programmes when 'unimodal' psychiatric or physiotherapeutic services do not suffice [8]. Nonetheless, patients had often been seen by their General Practitioner, but seldom accessed specialized behavioural or multi-modal treatment, and often believed that their complaints are inadequately managed (28-62%) [57].

3.2.2 Literature review

Efficient use of scarce resources and removal of access barriers are important motives for developing CBIs [16]. Results on the effectiveness of computer-based behavioural interventions are promising, but uncertainties regarding their actual usage certainly applies to FSS patients [16, 33]. Virtual reality and gaming

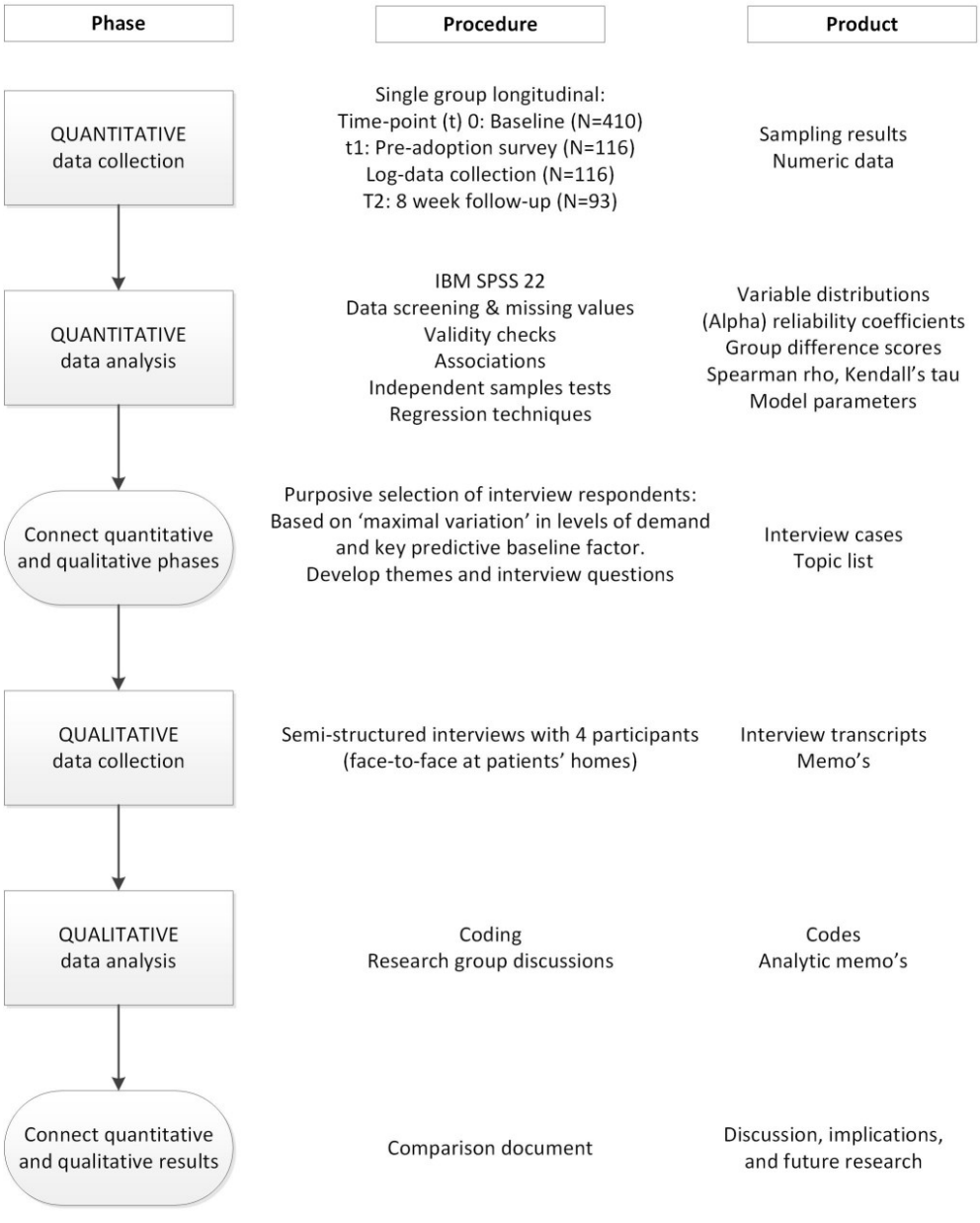
technologies have been serious for triggering positive emotions, distraction, or graded exposure in rehabilitation and pain management for improvements in physical functioning, pain symptoms, and daily life activities [179, 180]. However, there has been no evaluation of the effectiveness of serious gaming as an independently accessible means for delivering behavioural change messages to patients with FSS [30, 43, 44]. The actual extent and reasons of patient engagement in serious games will largely determine their impact [30]. A better understanding is needed of why CBI's have not been optimally used by which patients with chronic pain and fatigue symptoms to overcome the treatment barriers they face [16], and why integration of serious gaming can offer a partial solution [30].

3.2.3 Research goals

This study aims to explain usage of serious gaming and provide a comprehensive feasibility description from the perspective of adult patients with chronic pain and fatigue complaints. The opportunity to conduct this study was provided by the planned incorporation of the serious game 'LAKA' within a standardized multidisciplinary rehabilitation for adult patients with chronic and complex fatigue or pain symptoms in the Netherlands. The primary objective is to explain variation in the demand for serious gaming when offered for voluntary usage during a rehabilitation. Relationships are studied between usage (intentions), behavioural factors, and patient baseline characteristics, including case-mix, functional and clinical status, and medical history. In doing so, this study contributes to a better understanding of why serious games are demanded by patients in real health care settings.

Secondly, feasibility was thoroughly described to prepare for a full-scale evaluation in exploring the domains of acceptability, implementation, practicality, and promise for efficacy. Both research goals are reflected in a conceptual framework (See S2 Appendix, table 2.1) integrating technology acceptance modelling in a feasibility study design [23-27]. Overall, this contribution enables feasible proposals for incorporating and evaluating a serious game for behavioural change within the rehabilitation of patients with complex chronic pain and fatigue complaints.

Figure 1: Mixed-methods design overview



3.3 METHODS

3.3.1 Research design

A mixed method design was implemented with sequential quantitative (QN) and qualitative (QL) phases (see Figure 1) [181]. Due to the availability of adequate quantitative research instruments, an explanatory sequential mixed-methods design worked well for triangulation, illustration, and complementing QN findings with in-depth QL insights and with practically useful information about feasibility [182, 183]. The QN phase was prioritized and set up as a longitudinal single-group study of target patient responses to LAKA when offered for voluntary usage during the first 8 weeks of their programme. The QL phase provided a complementary inductive approach to both research questions. QN and QL phases were mixed in using QN results for the preparation of QL data collection, and again when integrating and documenting QN and QL results.

Textbox 1. Inclusion and exclusion criteria for study participants

Inclusion criteria:

- Between 18 and 67 years old
- Lives in the Netherlands, and is proficient in Dutch language
- Reports the presence of pain for more than 6 months, or fatigue complaints or a musculoskeletal disease for more than 3 months
- Had received previous primary or secondary health care services without a satisfactory result.
- Reported additional problems on at least 2 of the following problem areas: disturbance of participation, individual or environmental factors, psychological distress, and lack of spiritual well-being

(Potential) exclusion criteria:

- Presence of medical or psychiatric risk factors (non-treated medical condition, drugs- or alcohol addiction, and suicide risk)
- Presence of third party liabilities

3.3.2 Recruitment and data collection

Ethical approval of the protocol was obtained for this study (at the Psychological Ethical Testing Committee of Tilburg School of Behavioural Sciences, Tilburg University). 410 patients were eligible to start rehabilitation in one of four facilities of Ciran, a Dutch rehabilitation centre, between January 6th and April 6th 2014 (criteria are listed in textbox 1), and had given permission to process their diagnostic records for scientific research. Patients in this group were prompted on the day their first appointment with an e-mail invitation containing information

about the nature and consequences of participation in the study, and a link to the 'serious gaming page' (see S2 Appendix, Figure 2.1). This page guided patients through procedures of software access and additional data-collection. Local team leaders were requested to organize face-to-face reminders for patients about the study and the accessibility of LAKA regardless of giving informed consent.

Additional QN data had been collected from study participants with two surveys and log-file recordings (S2 Appendix, textbox 2.1 contains surveying details for routine and additional data-collections). The first survey was to be completed within four weeks after the invitation and before usage (t1). The second survey (t2) was added to a standard mid-term evaluation after 8 weeks, and was to be submitted to the 12th week. Participants' actual usage behaviour had been logged automatically between the pre- and post-surveys. In the intermediate phase, the focus was on "demand" as the primary subject of the study. Two extreme cases were selected so that a relationship between the most predictive baseline characteristic for the use of LAKA could be clearly illustrated. Two more cases were selected with demand levels that were poorly explained by this 'key' predictor, and more likely to provide information about omitted factors or counterfactuals. QN results were also used to set up an interview schedule. Purposefully selected participants were invited with a pre-scripted telephone call after their programme was finished. Interviews were held during 1 to 1.5 hour home visits, tape-recorded and transcribed. Field notes were taken, and full transcripts were sent to respondents by e-mail within a week after the interview.

3.3.3 Intervention

A standardized 16-week multidisciplinary rehabilitation programme was delivered by teams of physiotherapists, psychologists, spiritual counsellors, and medical rehabilitation specialists (textbox 2). A full description of the programme is provided by Garschagen et al. [184]. As recommended, functional requirements were specified before the modelling and evaluation of LAKA [186]. LAKA delivers skills training with metaphorical simulation elements (´encounters´), and guided exercises for focused attention and open awareness [40]. These elements are interspersed with images of real-world environments, immersive mini-games, and in-game debriefings for 'transferring' new insights beyond the virtual world (textbox 3).

Textbox 2. Characteristics of the multidisciplinary rehabilitation programme

Tailored: The programme has a modular build-up to match individual care need.

Outpatient, intensive: On average, 100 hours delivered by professionals (both individual and group sessions), and 30 self-directed hours

Integrated programme components:

- 45% Exercise therapy, graded activity, graded exposure, and education in physiology
- 15% Cognitive behavioural therapy
- 15% counselling and guidance in resuming participation in important life domains, such as work, social activities, and family life
- 25% spiritual education

Target outcomes:

- Primary: Improvement of well-being , and participation in important life-domains (activity and participation domains 4-9 of the International Classification of Functioning)[185]
- Secondary: Reduce pain, fatigue, and emotional distress symptoms

Textbox 3. LAKA design

Problem addressed: In complex cases, suffering associated with FSS has an intrusive impact on patients' existence and their interactions with caregivers, family, or friends.

Design team: The design team involved entrepreneurs, researchers, a scriptwriter, game designers, artists, programmers, audio experts, voice-actors, and IT specialists.

Stakeholder involvement: Feedback sessions (on functional specifications, theoretical model, and prototypes) involved experts (in behavioural science, medical technology, and spirituality), and critical users.

Genre: Singe-player adventure game.

Goal (of the game): LAKA was designed to provide a skills training in 'spiritual' practices. Practices are focused upon behavioural qualities that are associated negatively with negative emotions and positively with psychological well-being: 'generosity', 'moral discipline', 'patience/forbearance', 'enthusiastic energy', and 'mental stability'. Accordingly, the design includes the delivery of various behavioural change techniques integrated in an immersive simulation environment.

Main challenges (in the game): Identify with a personal Avatar, and engage in a quest. The story is about an Avatar, who learns about ´the art of living´ while traveling the world after a significant deterioration of his/her condition. Tasks primarily entail the consideration and evaluation of response options in virtual 'encounters' with non-playing characters.

Application components: Introduction, four training modules (or travel 'destinations': London, Turkey, Asia, Africa) with recurrent components, and a celebratory end.

Duration: Completing the game from start to end takes about 2.5 hours.

Game controls: Interaction design and controls (with computer mouse and keyboard) were designed for easiness. Progression in the game does not depend on gamer performance or skill.

Graphics: Mixed 2D/3D graphics with comical cut scenes.

Sound: Voice-overs and music convey emotions and atmosphere.

Platform: Personal computer or Laptop (MS Windows version).

System requirements: Windows XP or beyond, a 6 Giga-bytes hard drive, 1 Giga-bites memory, and

a stable internet connection.
Accessibility: Via the 'serious gaming' web-page by downloading, or by following instructions for picking up a Digital Versatile Disk (DVD) at local facilities.

S2 Appendix, Figure 2.2 and table 2.2, provide additional information (e.g., screenshots and playability feedback collected before this study). A Windows version of LAKA was offered for usage wherever and whenever convenient, and without support by health professionals. No recommendation for a minimum or maximum amount of usage was given, and no prompts or reminders were sent. On the one hand, it was expectable that many target patients would not use LAKA due to this non-committal mode of delivery. On the other hand, this variation was desired to discover explanations and practical suggestions that generally apply for delivery in open and clinical settings.

3.3.4 Measures

3.3.4.1 Demand, demand factors, and other feasibility domain outcomes

Objective indicators of demand were based on automatic data logs of participant activities: 'frequency' (number of days on which progress was logged), 'duration' (sums of time-intervals between log-ins and subsequent data logs), and 'progress' (the number of completed encounters). Demand was rated, before and after usage, by rates of agreement (1; completely disagree to 7; completely agree) with 3 statements about their current behavioural intention (BI) to use LAKA during rehabilitation [187]. Seven-point Likert scales were also used to assess behavioural factors, including performance and effort expectancies, social influence, perceived behavioural control, computer anxiety and self-efficacy, hedonic motivation or enjoyment, habit, and trust [187-190]. S2 Appendix, table 2.1, contains details about all survey measures, including variable definitions, items, validity, and reasons why behavioural factors may be relevant [190-195]. Practicality was indicated by counting log-ins of participants with positive behavioural intentions (BI at t1 >= 5) as evidence of success in obtaining the software, installation, and running the application. Study and usage attrition were interpreted as indicators of the degree of (study) implementation. Acceptability was operationalized as post-usage perceived appropriateness in enjoyment, ease, and knowledge improvement in participants who completed at least the first module of the game.

3.3.4.2 Baseline measures

Retrieved baseline variables were categorized into case-mix, functional status, clinical status, and previous treatment variables. Case-mix variables included gender, age, education level, environmental issues, and treatment facility. Preferred coping styles were measured with the Utrecht Coping List (UCL). Functional status variables included the duration and course of health complaints, employment status, absenteeism, and 1-item general subjective health. Pain intensity was assessed with a 11-point Numerical Rating Scale (NRS) [196]. The Checklist Individual Strength (CIS) was used to assess fatigue dimensions [197]. Clinical status variables included a categorization of the chronic symptom patterns by a rehabilitation specialist (primarily a fatigue, musculoskeletal, or other pain condition). Body-mass index and blood pressure were measured in physical examinations. Psychopathology dimensions were assessed with the Dutch 90-item Symptoms Check List (SCL'90) [198]. The Pain Coping and Cognitions List (PCCL) and Tampa Scale of kinesiophobia were used to measure pain coping and cognitions [199, 200]. The internal consistency was checked for all Likert-scale measures (see S2 Appendix, table 2.3). Finally, patients indicated previous specialized treatments and current medication intake.

3.3.5 Data analyses

3.3.5.1 Data exclusion

Cases were list-wise deleted before analysis if the proportion of missing observations was less than 5%, or handled by predicting five data imputations for each empty cell through regression of all variables in the dataset (using the MCMC algorithm). All full-case QN findings presented as marked results are supported by pooled results.

3.3.5.2 Participant statistics

Characteristics of eligible patients, study participants, and participants who logged into the game ('players') are described by descriptive statistics and frequencies. Chi square and Mann-Whitney-U tests were used to compare baseline level characteristics between study participants and participants who logged-in in LAKA, versus eligible patients that were not included in those groups. Similarly, differences were tested between participants who logged in vs. participants who did not log-in.

3.3.5.3 Process analyses of demand and feasibility descriptions

All feasibility outcomes of serious gaming during the first 8 weeks of the programme are indicated with descriptive statistics and line-graphs. Association measures (Spearman rho and Kendall's tau statistics) between baseline characteristics, behavioural factors, and feasibility outcomes were calculated and tested for significance. Moreover, multiple (ordinary least squares) regression analyses were performed for the sequential identification of important constituent factors of behavioural intention at t1, to explore whether effects of behavioural factors differed between sub-groups of patients (see S2 Appendix, Figure 2.3), and to test if marked associations between baseline characteristics and behavioural intentions were (fully) mediated by behavioural factors [201].

3.3.5.4 Qualitative data analysis

Interview transcripts were coded by one author (MV) using a software package: MAXQDA 11. In a first coding step, all text fragments about the specified interview topics were labelled with short statements that corresponded with contextual meanings. A second author (MJ) independently repeated this first coding step for one interview. These 'first order' codes were compared, and discussed between MJ and MV to align and refine the coding procedure. In a second coding step, more abstract categories were generated. Throughout this process, first order codes and emergent categories were constantly compared and hierarchically structured as a means for critical appraisal and to avoid imposing preconceived ideas on the QL data. Finally, categories were related to one another by designating them as context factors, conditions (barriers or facilitators), events/interactions, or consequences.

3.3.5.5 Mixing quantitative and qualitative results

In connecting QL and QN findings, codes and statistics were provided for comparison for both research questions. QN results were deemed notable for comparison with QL findings if *P*-values were below .05. Subsequently, three researchers (MV, MJ, and HV) discussed and determined points of convergence, divergence, or complementariness between QN and QL findings. In doing so, observations were summarized to determine which, and to what extent remarkable and solid QN findings were clearly illustrated and triangulated. Moreover, the point at which qualitative data collection was stopped was

determined on the basis of saturation with respect to illustrations of behavioural factors and the role of a key predictive baseline characteristic for usage in early stages.

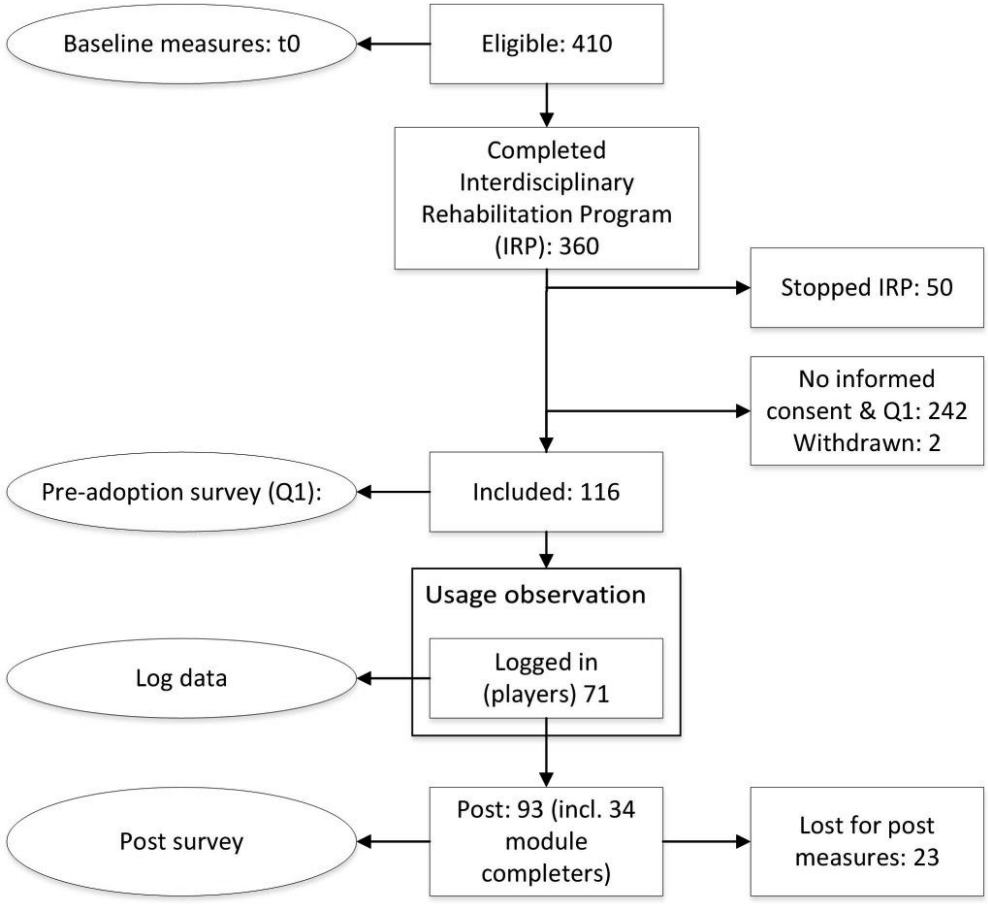
3.4 RESULTS

3.4.1 Participant statistics

Of the 410 invited eligible patients, 32.2% provided informed consent and completed the first additional survey (Figure 2). The 84 patients who reported why they did not wish to participate often mentioned 'other obligations' (23), 'facilitative problems (14)', 'not enough energy or concentration (13)', and 'no intention to use the intervention (14)'. One patient withdrew because of a broken computer, and one for experienced too much hindrance in attempting to use an unsupported web-browser. The second questionnaire was submitted by 93 participants (80.2%).

Study participants' average age was 44.4 years (SD 10.8), and ranged between 21 and 63. Seventy-one percent was female (table 1). Sixty-nine participants were completely absent from work. Average length of absenteeism amounted 157 days (SD 223.0), with a median just over 100 days. Forty-seven participants (40.5%) reported moderate to severe pain (5 to 10), and 108 experienced problematic fatigue. Average scores for depressive (42.9, SD 11.4), and anxious (22.2, SD 8.2) symptoms were high. Participants had been regularly surfing the internet, but only 46 patients (39.7%) had been playing a computer over the past year.

Figure 2. Flow diagram of study participants



No statistically significant differences between participants and non-participants were found for case-mix variables (S2 Appendix, table 2.4). However, patients with more severe pain symptoms were underrepresented in the sample. The proportion of patients who had received specialist treatment for their current complaint was lower in players than in non-players (Chi-square=4.120 *P*=.042).

The group of 71 who actually logged-in (players), reported relatively higher scores for coping through active engagement and social support seeking, lower scores for pain coping, and fewer presence of environmental issues.

Table 1. Characteristics of study participants (n=116).

Characteristic[1]	Category	Data N (%)
Demographics		
Gender	Female	71 (61.2)
Age	< 35 years old	23 (19.9)
	35 - 45	30 (25.9)
	45 – 55	41 (35.3)
	55 – 67	22 (19.0)
Education level ISCED[2]	Primary or less	32 (25)
	Lower to post-secondary	44 (37.9)
	Tertiary and post-tertiary	40 (34.5)
	Missing	3 (2.6)
Functional Status		
Employment in paid work	Full-time	49 (42.2)
	Part-time	52 (44.8)
	None	15 (12.9)
Absenteeism	Not	15 (26.1)
	Partially	17 (14.8)
	Completely	69 (59.1)
Duration of absenteeism for present somatic symptoms	< 3 months	31 (26.7)
	0 - 3 month	41 (35.3)
	3- 6 months	22 (19.0)
	6-12 months	14 (12.1)
	1-2 years	6 (5.2)
	More than 2 years	2 (1.7)
CIS Physical activity[3]	Below average	67 (58.8)
Symptoms		
Symptom duration	< 3 months	3 (2.6)
	3-6 months	11 (9.5)
	6-12 months	30 (25.9)
	1-2 years	27 (23.3)
	>2 years	45 (38.8)
Pain NRS[2]	No pain (0)	18 (15.5)
	Mild pain (1-4)	51 (44.0)
	Moderate pain (5-7)	36 (31.0)
	Severe pain (7-10)	11 (9.5)
Fatigue	No fatigue (NRS[2]=0)	2 (1.7)
	Not problematic (CIS[2] <=76)	6 (5.3)
	Problematic (CIS>76)	108 (94.7)
CIS Subjective fatigue[3]	Above average	50 (43.1)

SCL-90b Depression[4]	(Below) average (16-31)	24 (20.7)
	Above average (32-35)	7 (6.0)
	High (36-52)	63 (54.3)
	Very high (>= 53)	22 (19.0)
SCL-90 Anxiety[4]	(Below) average (10-17)	42 (36.2)
	Above average (18)	7 (6.0)
	High (19-28)	39 (33.6)
	Very high (>= 29)	28 (24.1)
Primary diagnosis	Chronic musculoskeletal disorder	21 (18.1)
	Chronic pain	17 (14.7)
	Chronic fatigue	78 (67.2)
Previous treatment		
Medical specialist treatment	Yes	70 (60.3)
Medication usage	Yes	80 (69.0)
	Missing	1 (.9)
Previous use of similar technology		
Habit of frequent internet usage with a pc or laptop	On 6-7 days per week	84 (72.4)
	On 3-5 days per week	22 (19.0)
	On 1-2 days per week	9 (7.8)
	On less than one day /week	1 (0.9)
Experience of digital game play	Never played a digital game	37 (31.0)
	More than a year ago	33 (28.4)
	Less than a year ago	14 (12.1)
	Less than a month ago	32 (27.6)
Habit of frequent digital game play	One or more times per month (and less than a month ago)	29 (25)

[1] A selection of individual baseline characteristics is presented to facilitate comparison with previous evaluations of behavioural interventions for FSS patients.
[2] Abbreviations: ISCED Highest education levels (Dutch system) were rescaled in accordance with the International Standard Classification of Education (low: 0-1, middle: 2-4, high: 5-6). NRS Numerical Rating Scale. CIS: Checklist Individual Strength. SCL: Symptom Checklist.
[3] For all participants (2 missing values were ignored; n=114). Compared to average in a population of patients with chronic fatigue syndrome
[4] Compared with a population of Dutch patients with chronic pain [49]

Four interview respondents were selected based on their combination of scores for coping by active engagement and demand (table 3). Open questions were asked to introduce and focus on topics (see S2 Appendix, textbox 2.2). Two topics addressed the primary research question, namely “initial response” to the digital game offering (1), and patient “experiences” throughout their interactions with LAKA (2). The second topic and a third topic: “suggestions for improvement” (3),

served to collect complementary information on feasibility domains. After a first round of mixing, four interviews was deemed sufficient to provide clear illustrations of the most notable QN explanations for demand.

3.4.2 Process of demand

3.4.2.1 Direct effects

Actual usage indicators measured at pre-adoption were associated with behavioural intention at a moderate level at t1 (ρ= .527 - .546), and weakly at t2 (ρ= .260- .273). Behavioural intention was associated with various behavioural factors measured at t1 (table 4).

Table 3. Characteristics of interview respondents

Characteristic	**Respondent**[1]			
	1	2	3	4
Session days, encounters	3, 20	0, 0	1, 1	2, 4
Behavioural intention	6	1	4	7
UCL Active coping[2]	Very high	Very low	Very high	Average
Gender	Male	Male	Female	Female
Age	35	57	62	54
Work status	No paid work	Fully absent for 97 days	Fully absent for 287 days	Present at work
CIS Fatigue severity	>36	Above average CFS[3]	Above average CFS	>36
Pain NRS	3	1	3	0
SCL Anxiety	Average	< Average	High	High

[1] Respondents were identified by inspection of a bivariate scatterplot displaying the most predictive individual baseline characteristic on the x-axis, frequency of usage on the y-axis, and marking dots representing negative (<3), neutral (3-5), and positive (>5) behavioural intentions at t1.

[2] Levels of active engagement within the sample are similar to healthy worker population levels. Norm scores are slightly different for males and females.

[3] As compared to average fatigue severity in a sample of patients diagnosed with chronic fatigue syndrome.

Table 4. Associations between behavioural factors and behavioural factors

Factor[1]	**Association**					
	Factor (t1[2]) with BI[1] (t1) n=115/116[3]		Factor (t1) with BI t2) n=92/93		Factor (t2[2]) with BI (t2) n=32/34	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
PE (ρ[4])	.33	<.001	.19	.08	.59	<.001
EE (ρ)	.42	<.001	.10	.37	.35	.045
SI (ρ)	.14	.13	.17	.11	.42	.01
PBC (ρ)	.33	<.001	.04	.71	.22	.22
TR (ρ)	.31	.001	.21	.049	.53	.001
HM (ρ)	.54	<.001	.43	<.001	.61	<.001
CA (ρ)	-.27	.003	.10	.35		
CSE (ρ)	.22	.02	.32	.002		
HB (τ[4])	.22	.007	.06	.53		
PKI (ρ)					.77	<.001

[1] BI: Behavioural intention, PE: Performance Expectancy, EE: Effort Expectancy, SI: Social influence, PBC: Perceived Behavioural Control, TR: Trust, HM: Hedonic Motivation, CA: Computer Anxiety, CSE: Computer Self-Efficacy, HB: Habit, PKI: Perceived Knowledge Improvement

[2] t1: assessment at pre-adoption, t2: assessment after 8 weeks of access to serious gaming

[4] Pair-wise deletion: one respondent submitted an incomplete web-survey at t1.

[5] ρ: Spearman Rho, τ: Kendall's Tau (for dichotomous variable)

*Table 5. Parameters and model fit of multiple regression models for constituent factors of behavioural intention at pre-adoption (*115 respondents*).*

Factor[1]	**Model**							
	Core TAM[2]		UTAUT[2]		Core + HM[1]		Core + HB[1]	
	CF[3]	*P*-value	CF	*P*-value	CF	*P*-value	CF	*P*-value
Constant	.84	.15	.34	.63	.89	.10	.69	.23
PE (b)	.40	.002	.35	.01	.04	.79	.46	<.001
EE (b)	.52	<.001	.51	<.001	.27	.02	.47	.001
SI (b)			.15	.09				
PBC (b)			.06	.63				
HM (b)					.59	<.001		
HB (b)							.63	.02
Model (ΔR^2)	.34	<.001[4]	.36	.22[4]	.43	<.001	.38	.02

[1]PE: Performance Expectancy, EE: Effort Expectancy, SI: Social influence, PBC: Perceived Behavioural Control, HM: Hedonic Motivation, HB: Habit, PKI: Perceived Knowledge Improvement

[2] TAM; Technology Acceptance Model, UTAUT; Unified Theory of Acceptance and Use of Technology, PE; Performance Expectancy, EE; Effort Expectancy, SI; Social influence, PBC; Perceived Behavioural Control, HM; Hedonic Motivation, HB; Habit

[3] CF: Coefficient

[4] *P*-value of additional variance explained over a constant only model, or over the 'core' TAM model.

Effects of perceptions on performance, social norms, and knowledge improvement became stronger over time and exposure to LAKA. Expectancies of effort and performance independently shared a significant amount of variance with behavioural intention at t1 (table 5). Second step models were superior to the core model if supplemented with hedonic motivation or habit, but not if other factors were added. Inclusion of hedonic motivation weakened the effects of core factors such that performance expectancy was no longer a significant factor for behavioural intention.

If asked openly for an explanation of their own initial response to the offer to play LAKA during rehabilitation, respondents first explained their affect or attitude at that time, such as their openness to try the intervention. These feelings were substantiated by memories of previous experiences with computer game play. Those who felt positive about using the game did not experience barriers in concerns about privacy, usefulness, opinions of others, or a lack of resources. Nonetheless, respondents desired an explanation about how the intervention could bring about personal benefit.

"I do like games. I have them myself… I'm just going to see what it is. Not immediately: no, I do not join in… I was just open minded… With two or three people I have talked about it (eds.: study, LAKA), and they said: the only thing for which I look at the computer, is to see what time I should be here. For other things; let me know…" (Respondent 4)

"I did not recognize a goal… If there was a little more explanation, then I would have probably played ... and especially if it helps". (2)

Various associations between case-mix variables and demand indicators were marked (See S2 Appendix, table 2.5). Frequency of coping by active engagement and comforting thought were positively related to demand before exposure. Associations between demand indicators and social support seeking increased by exposure. Behavioural intention BI was significantly lower for participants treated in location A, while participants treated in location D progressed more within the game. Behavioural intention measured after 8 weeks was associated negatively with education level, and positively with age. Notable differences in demand by

functional and clinical status variables were observed as well. LAKA was played more frequently by participants that reported partial absenteeism from work and lower pain coping scores. More usage was registered in players with higher levels of perceived competence in their job, symptom deterioration, higher pain intensity, lower internalization, and less symptoms of anxiety at baseline.

Three interview respondents who exposed themselves to LAKA explained their level of engagement by witnessing that game tasks were welcome challenges in early stages of a rehabilitation process. However, patient users' attention shifted away from gaming tasks towards the ('slow') pace and structure of the game when their confidence and engagement in 'real-life' roles increased. For example, noticing that selecting preprogramed alternatives is not as complex as responding in real life, and purposively selecting 'bad' responses to explore the 'rules' that guide scenarios. Disengagement was also explained the belief of being incapable to perform a certain task.

"At the time of the programme… I was on sick leave. What could I do? I really had time for the computer, and no energy for anything else... When I stopped, it was enough for me. The game is too slow for me… For my energy that I've built up again... I started working again. I'm going to a sports club. Yes, my life, my rhythm, is different... I have no time" (3)

"In work, I am constantly adjusting to people. So for me it did not really matter… I have an ADHD problem. So, attention exercises are a disaster for me. I have no patience for that… The first time I went on to see where I got stuck when I was just giving 'wrong' answers… Occasionally, when you had to wait, I was like: come on, hurry." (1)

3.4.2.2 Moderation and mediation effects

Performance expectancy was a significantly stronger predictor of behavioural intention at t1 in patients primarily diagnosed with chronic fatigue rather than a chronic pain condition (Beta=.98, *P*<.001), and high levels of depressive symptoms (Beta=.91, *P*=.006). The relationship between social influence and behavioural intention was affected negatively by the more than 6 months absenteeism (Beta=-.61, *P*=.01). The presence of daily internet usage over the past year strengthened

the positive effect of hedonic motivation on behavioural intention at pre-adoption (Beta=.63, *P*=.001). The negative association between computer anxiety and behavioural intention was significantly weaker in participants younger than 45 years old (Beta=.42, *P*=.009). Mediation analyses showed that perceived behavioural control mediated the effect of active engagement on behavioural intention at pre-adoption, but did not the effect of active engagement on the presence of a log-in.

Focusing on individual differences in coping with the delivery of LAKA during interviews yielded self-descriptions by patients varying between being 'curious, a gamer, and capable' to play, versus being neither a 'games person' nor an 'early adopter' and believing that computer games are hard.
"Anyway, I am someone who games a lot ... Did not doubt about being able to play it. I am someone who wants to follow and keep up with things ... There are buttons, and all the buttons I want to have tried them at least once." (1)

"Most games that happen to PCs, such as Tetris and things like that… That is under time pressure … No, that does not attract me and I cannot do that ... I'm not the pioneer to go on my own." (2)

3.4.3 Feasibility description

3.4.3.1 Demand

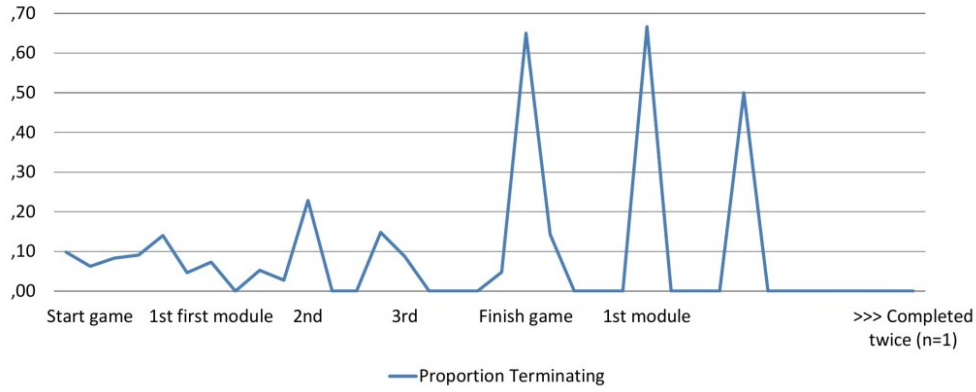
At the pre-adoption stage, most participants had a moderately positive intention to use LAKA in the next 4 months in addition to their scheduled programme activities (table 7). Nine participants (7.8%) with low initial behavioural intention (2 or lower) were statistical outliers, but not excluded for further analyses. Behavioural intention decreased over the course of 8 weeks. On average, players completed 8 encounters, which equals two out of the four modules in total. The first module of the game was completed by 40 patients (56.3%). Twenty players (28.2%) completed the game from start to end. A line graph (Figure 3) shows that players were more likely to stop using the game when they headed for a new game, module, or element.

Table 7. Descriptive results of demand level assessment

	N[1]	Mean	Median	SD	Min	Max
Behavioural intention (t1)[1]	116	5.1	5	1.4	1	7
Behavioural intention (t2)[1]	93	3.5	4	2.0	1	7
Session days	71	1.8	2	1.4	0	6
Time spend	71	1:14:40	0:52:25	1:07:42	0:00:00	4:22:27
Progression	71	8.1	7	7.3	0	32

[1] n: number of observations, t1: assessment at pre-adoption, t2: assessment after 8 weeks of access to serious game

Figure 3. The proportions of players who stopped using LAKA at certain stages of progress.



3.4.3.2 Implementation and practicality

Fifty-nine of 85 participants (69.4%) with a positive intention to use (BI >=5) logged-in successfully. In treatment facility A, 12 of the 24 willing participants logged-in, which is significantly less (Chi square= 5.935; *P*=.015) than in the other three locations (70.6 - 81.0%). Players who possessed more computer platforms (i.e., tablet, console, smartphone) progressed less within the game (ρ=-.39, *P*=.001). Most activity was recorded during the first 4 weeks of rehabilitation (Figure 4). When playing at home, participants logged in at different times during the day, but mostly after 6 p.m. (Figure 5).

Figure 4. Sums of logged in-game activities throughout the first twelve weeks of multidisciplinary rehabilitation.

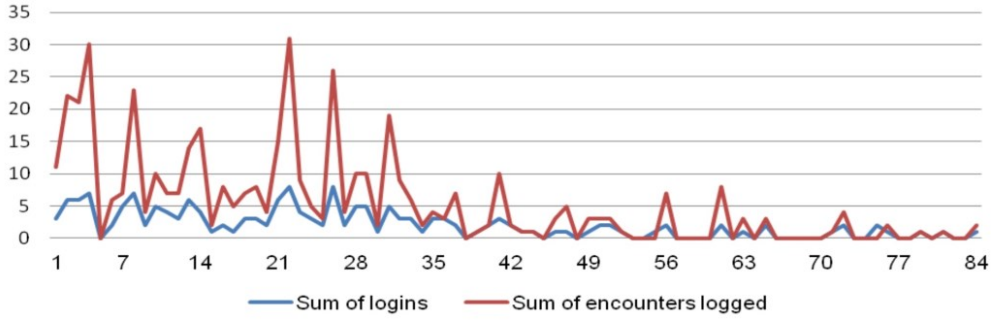
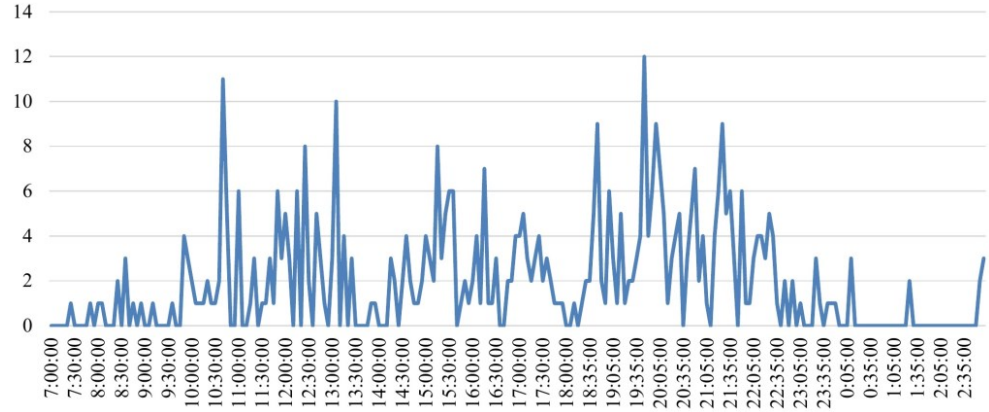


Figure 5. Number of log-ins by participants by time of the day.



3.4.3.3 Acceptability and potential for efficacy

Post-usage perceived ease, rated by those who played the first module of LAKA, was moderately high (mean 5.4/7, SD 1.54; median 6/7), and varied positively with baseline active engagement (ρ=.45, *P*=.007), motivation (ρ=.57, P=.001), and indication of a chronic musculoskeletal disorder (*P*=.008). Perceived enjoyment levels were moderately positive (mean: 4.6, SD 1.7), and positively associated with baseline concentration problems (ρ=.44, *P*=.01). Post-usage perceived knowledge improvement (mean: 4.6/7, SD 1.8) was lower in participants with higher a Body Mass Index (ρ=-.42, P=.02).

Interview respondents who played LAKA (1, 3, and 4) believed that it was a suitable programme component. A variety of game elements were appointed that

were liked. Furthermore, tasks were quickly understood, taken seriously, and experienced as a fit with the approach taken in other programme components. 'Encounters' were recognized as representations of real-life situations. Respondents who played, generally believed that they could select options that corresponded with their intentions. Experienced consequences were acquaintance with meditation, concentration and reflections on ideal and 'healthy' selves, rumination, and on adequate ways of responding.

"I saw pretty quickly where they wanted to go with it. In that respect, it does well with what they do at <the clinic>" (1)

I have a computer, then it is no problem… I could use that game well… Later you find out: oh, it's not just a game. It is something to think about your own situation... Then you're not in the game, but you are in reality… All kinds of possibilities were offered (referring to response options in encounters): what I see as negative, in between, and what I see as 'good'… It was also a bit about … as I was during the illness... I could recognize myself in some situations: Yes, that was the old <patient name>… At the moment however, I react completely differently. I could see that. Maybe that also influenced me: my healing" (3)

"During the game you were forced to concentrate; not wanting to go through it too fast… Actually you were just forced to use your concentration... It occurs to me that I ruminate long about something, and it also confronts you with that… Those first meditation exercises… I really needed to do it a few times ... That got me meditating…" (4)

3.4.4 Suggestions for improvement

Respondents suggested to integrate LAKA, like other programme elements patients normally adhere to. Additional support was desired by means of a personalized introduction early in the programme, information about how to get something out of the game and about what is achieved afterwards, professional feedback on situations in the game, and facilities for gaming at treatment sites. A suggestion for playability was to match the pace of in-game interaction with skill or health status. Software support should be extended to multiple platforms.

"I would certainly continue to offer it. Maybe someone should be designated to introduce it at an early stage... To show it, and to show what you can get out of it for yourself. In a playful way ... If an entire manual should be read, then you put it away quickly… Actually, I do most with the IPad. If that is possible... I rarely use a pc."(4)

I would let everyone play. I think if it is offered in <location name>... "If there is a psychologist… that is better. Immediately talk about those reactions taking place at that time… find out faster what kind of situations played a role in becoming so ill, and get better... Maybe you could combine it … a bit slower in the beginning and a little faster at the end". (3)

3.5 DISCUSSION

3.5.1 Principal findings

This study primarily questioned why, and by which patients with chronic pain and fatigue complaints, serious gaming for behaviour change is demanded during a multidisciplinary rehabilitation programme. Voluntary serious gaming (LAKA) was generally explained over time by perceived enjoyment and ease. Coping resources are important to solve delivery issues, get in control, and start using a serious game. Patient environment, health status and performance expectancies were relevant factors for the usage of a serious game in conjunction with time, and/or exposure.

Secondly, feasibility was described in preparation for a full-scale evaluation. A substantial number of patients played the game under non-committal conditions. According to them, LAKA will be acceptable and useful. Active ingredients were recognized and deemed to be relevant in early stages of a rehabilitation process. Patients suggested to deliver the game with social support through early and expeditious communication about how and when the game is relevant for their rehabilitation, and with extended (technical) facilities.

3.5.2 Strengths and limitations

This study provides the first empirical results on a novel serious game for behavioural change in patients with chronic pain and fatigue complaints. Comprehensive information is presented on processes of self-selection,

acceptance and attrition, which provides rare insights in risk factors for bias in CBI evaluations [202]. Mixed methodology strategy worked well to triangulate QN findings with newly collected QL data. Important demand explanations are based on notable and robust statistical results backed-up by a decent sample size, and clear illustrations with QL data. QN results that were not clearly illustrated with QL data, or based on more selective patient samples, provided practical information and clues for future research. More than a final feasibility assessment, this study contributed with general and utilizable knowledge for the future deployment of serious gaming for FSS patients in practice.

Limitations should be considered for drawing general conclusions about the feasibility of serious gaming for FSS patients. Feasibility was not assessed against a control group level or reasonable benchmark. Technology acceptance measures are commonly used, but they are often contextually adapted and serve theory building rather than feasibility assessment. Furthermore, the study builds on pragmatic eligibility criteria and convenience sampling of Dutch patients. It cannot be ruled out that early judgments about the nature of the delivery mode affected results via self-selection. Performing a large amount of explorative statistical tests threatens statistical power and internal validity. Caution should be exercised for interpreting causality in relationships between behavioural factors and behavioural intentions, because independent and dependent variables were measured at the same point in time, and hedonic motivation was not clearly distinct from performance expectancies and behavioural intentions. Whether the use of technology acceptance questionnaires alone would be appropriate method for assessing the usage of Gaming technology, especially at a time when patients may have difficulty processing information, can be doubted and is not recommended. Finally, advanced statistical techniques like Partial Least Squares regression [203], and/or newer process analyses techniques [204] would have suited well, but were not used. QN method limitations were addressed by triangulation of key QN findings with QL data, comprehensive sample description, validity checks, residual analysis, and sensitivity analyses (for outlier removal, measures of association, and regression method) (see S2 Appendix, textbox 2.3).

3.5.3 Comparison with prior work

Researchers have stressed that a better understanding of the demand for CBIs is a concern in overcoming barriers to treatment of patients with chronic pain and fatigue symptoms [60, 64]. To our knowledge, this is the first empirical study of serious gaming for the delivery of behavioural intervention for patients with chronic somatic symptoms and functional problems. Findings suggest that voluntary engagement in serious gaming is strongly driven by positive affect. The importance of hedonic motivation for demand is remarkable, because this is an often omitted factor in previous research on the use of information technology in health care [190]. Concerns about utility, demonstrability of results, privacy, or consultation of important others seemed to have a limited impact on demand in this case, when patients had no previous experiences. Ubiquitous interview quotes about "openness" hinted that inclinations to search for meaning or personal growth could partially explain demand for serious gaming [205, 206]. Concluding that FSS patients will use a serious game 'for the sake of the activity itself' is tentative. Serious gaming interventions are relatively new and barely institutionalized, and limited information was available to patients about the efficacy of LAKA or a similar game. It could also be that patients thought about usefulness and trustworthiness of care before selecting the rehabilitation centre. Moreover, influences of individual differences in coping styles and perceptions of control and ease on the usage of LAKA corresponds with earlier work that found a positive effect of internal locus of control on the adherence to a web-based positive psychology intervention [168]. Such results might also reflect differences in executive functioning or capacities for self-control [207].

Other remarkable QN results, which were not clearly illustrated with QL data, are discussed in connection with past research, and/or as areas of future research. Findings on the effect of depressed mood on CBI usage have been mixed [183]. This study pointed in the direction of a negative relationship, but found no statistically significant direct effect. This might be due to the comparatively high levels of psychopathologic symptoms of these FSS patients [208]. A moderation effect is suggested by extremely low behavioural intentions that were found exclusively in patients with low to neutral performance expectancies and high levels of depressive symptoms. Furthermore, computer anxiety and experience might explain differences in relationships between age and technology usage

found in earlier studies [190]. Moreover, patients with lower scores for pain intensity and patients indicated with fatigue as their primary complaint were more likely to self-select as a player, while patients with higher pain intensity had been playing more once exposed. Further research on the usage of CBIs could focus on understanding 'matches' between symptom characteristics, 'readiness', and demanded delivery mode of behavioural treatment for FSS populations [209]. Another research focus can be patient-environment interactions (i.e., dealing with issues at home, absenteeism, and return to work) as barriers and facilitators for demand within this target group. For informing design and implementation of computer- and game-based modalities, it is useful to proceed with qualitative research, as well as by formulating and testing theoretically informed hypotheses on how usage varies by patient-, programme design, behavioural, and context factors [202, 210-212].

The degree of implementation of LAKA for eligible patients is not satisfactory, as could be expected when a CBI is offered under 'ad libitum' conditions. Besides blending with face-to-face delivery and multi-platform distribution, solutions for additional support can be provided through web-based features such as tailored messages, prompts, and support via e-mail, chat, or message-boards [163]. Acceptability and limited efficacy outcomes should be treated with caution, but suggest that LAKA is potentially efficacious, and engaging enough to complete once or twice (2-4 hours). Moderately positive enjoyment by users may reflect that the design principle of LAKA was not entirely hedonic, maybe at the expense of 'playability' aspects [213]. Eliciting reflective and meditative states LAKA was pleasant for a patient with concentration problems, but seems to go at the expense of adjustment to changes in satisfactory speed of interaction. Moreover, the game appears to provide opportunity to realize ideal selves, which supports intrinsic motivation [206]. However, LAKA also triggered serious reflections about discrepancy with 'actual' selves, which is associated with somatic symptoms and negative emotions [214]. 'Slowness' was mentioned as a reason for disengagement, but self-awareness was not. One may also reflect about how self-awareness in virtual reality relate to bodily and behavioural representations of Avatars [215], because extremely low perceived knowledge improvement levels were exclusively reported by patients with high BMI levels at baseline. High quality and adequately powered studies on the effects of LAKA and/or similar

systems on functional domains are needed, and could clarify the roles of (self) conscious and affective states, learning, and degree of engagement [30, 43, 216].

3.5.4 Conclusion

Although these first empirical findings support that a serious game is used by FSS patients for enjoyment and convenience, it became very clear that many patients will not be reached with a behavioural intervention of this modality under non-committal conditions. Social factors remain highly important for reaching many patients. LAKA will be feasible as a short and early intervention for patients by adjustments of social and/or technical support. A next step in deployment and evaluation of the efficacy and (cost-) effectiveness of LAKA in a controlled study is recommendable.

Abbreviations:

- **BI:** Behavioral intention
- **CBI:** Computer-based interventions
- **FSS:** Functional somatic syndromes
- **QL:** Qualitative
- **QN:** Quantitative

4 Outcome and process evaluation protocol

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Title: Serious gaming during multidisciplinary rehabilitation for patients with complex chronic pain or fatigue complaints: study protocol for a controlled trial and process evaluation

4.1 ABSTRACT

Introduction: Many individuals suffer from chronic pain or functional somatic syndromes and face boundaries for diminishing functional limitations by means of biopsychosocial interventions. Serious gaming could complement multidisciplinary interventions through enjoyment and independent accessibility. A study protocol is presented for studying whether, how, for which patients, and under what circumstances, serious gaming improves patient health outcomes during regular multidisciplinary rehabilitation.

Methods and analysis: A mixed-methods design is described that prioritizes a 2-armed naturalistic quasi-experiment. An experimental group is composed of patients who follow serious gaming during an outpatient multidisciplinary programme at two sites of a Dutch rehabilitation centre. Control group patients follow the same programme without serious gaming in two similar sites. Multivariate mixed modelling analysis is planned for assessing how much variance in 250 patient records of routinely monitored pain intensity, pain coping and cognition, fatigue, and psychopathology outcomes is attributable to serious gaming. Embedded qualitative methods include unobtrusive collection and analyses of stakeholder focus group interviews, participant feedback, and semi-structured patient interviews. Process analyses are carried out by a systematic approach of mixing qualitative and quantitative methods at various stages of the research.

Ethics and dissemination: The Ethics Committee of the Tilburg School of Social and Behavioural Sciences approved the research after reviewing the protocol for the protection of patients' interests in conformity to the letter and rationale of the applicable laws and research practice (EC 2016.25t). Findings will be presented in research articles and international scientific conferences.

Trial registration: A protocol for the naturalistic quasi-experimental outcome evaluation was entered in the Dutch trial register (NTR6020).

4.2 INTRODUCTION

4.2.1 Background and rationale

Video games are vividly debated to their behavioural and clinical outcomes, which may be negative or positive depending on game content and player attributes [43, 217]. Serious (health) games primarily target promotion of health benefits [30]. A new serious game, called LAKA, aims to facilitate patient learning about living with complex chronic somatic complaints [218]. Based on the results of a feasibility study, LAKA is deployed in a regular health care setting, as an additional component of outpatient multidisciplinary rehabilitation. The current protocol presents an innovative mixed-methods study for gaining insight into the effectiveness of serious gaming as a complementary modality during regular multidisciplinary rehabilitation.

Using a variety of definitions and measures of pain and disability, the worldwide prevalence estimates for chronic pain range between 7% and 64% [57, 219-222]. Individuals are in chronic pain (CP) when complaints persist beyond the usual 3 to 6 months of organic recovery [9]. Functional somatic syndromes (FSS) are diagnosed in individuals that seek medical help for functional disturbance and chronic somatic symptoms without a satisfactory explanation by organ pathology or disease [177]. CP and FSS may have a biological explanation in central nervous system sensitization [223, 224]. Predisposition to these disorders is probably determined by a combination of genetic factors and personality characteristics [225, 226]. Symptom patterns are often precipitated by trauma or social factors [8, 227, 228]. Maladaptive thoughts, feelings, and behaviour are assumed to maintain the symptoms [8, 229-231]. Regarding treatment, support has been found for a stepped care approach with active bio-psychosocial treatment when mono-disciplinary treatments are insufficient [8]. Randomized controlled trials that compared symptoms and functioning after multidisciplinary rehabilitation versus alternative treatments in patients with CP or chronic fatigue syndrome generally reported up to medium-sized differences [14, 232-234]. Nonetheless, recent research addresses improvement of bio-psychosocial intervention models [19, 184], ‘matching’ and ‘blending’ therapeutic strategies and delivery modes [18, 235], and promotion of patient engagement [54]. As such, access, reach, adherence and effectiveness of bio-psychosocial interventions may be enhanced.
Serious gaming could be of aid here. Previously investigated strategies are ‘exergaming’ to improve motivation for physical activity [236], ‘brain training

games' against dullness in the remediation of cognitive functions [237], 'virtual reality' for safety in graded activity or exposure [238], and 'health behaviour gaming' for fun while addressing behavioural antecedents [30]. In the fields of rehabilitation and pain management, virtual environments have shown promise in reducing acute pain by distraction, or in activity management to restore physical functioning [180, 239]. Despite of promising results for various mono-disciplinary applications of gaming and simulation, no evident application seems to exist for supporting biopsychosocial adjustment processes in patients with CP or FSS [30, 43, 44, 180, 237-240]. Outcome improvement after treatment in CP or FSS patients may be mediated by changes in aspects of self (beliefs about illness and fear avoidance, catastrophizing, and psychological flexibility), coping behaviour, and affect [83, 241]. Features that distinguish serious games from traditional modes include covert learning techniques, interactivity, storytelling, sound effects, visuals, and 'debriefings'. They could offer relative benefits for behavioural change processes through distinctive attentional (presence), affective (enjoyment), and meta-cognitive processes [242-245]. Further research into gaming mechanisms is needed [244], and may also inform about how biopsychosocial intervention mechanisms could be strengthened'.

However, within the outcome evaluation of multidisciplinary interventions several complicating factors arise. These consist of outcome multidimensionality and dependency on implementation in actual health care settings [47, 78]. In other words, characteristics at the levels of organization, care providers, patients and interventions all affect outcome levels [17, 246]. Therefore, ideally, multiple sources of information are used to evaluate to what extent, for whom, when and under what circumstances an innovation of multidisciplinary treatment improves outcomes in patients with CP or FSS [247, 248]. For example, some intervention studies show different outcomes of a computer delivered therapy when applied in different countries [149]. This is also an important issue for the outcomes of serious gaming, which are clearly sensitive to context factors [249, 250]. Therefore, 'debriefings' are suggested as a method for discussing and exploiting game-play experiences and strengthening learning outcomes [251]. Previous studies leave uncertainties about how to effectively organize instructional support, i.e. via software or delivered by (trained) health care staff, via internet or face-to-face, in groups or individually. There is strong consensus that adequately powered clinical trials are needed to determine the effectiveness of serious

gaming [30, 43, 44]. Moreover, pragmatic trials and realist evaluation principles are needed to determine how serious gaming relates to patient outcomes depending on how it is deployed in actual health care settings.

4.2.2 Study aims

Here we describe the protocol for outcome and process evaluations of complementary serious gaming during regular multidisciplinary rehabilitation for patients with CP or FSS, which holds three study aims.

The first aim is to investigate the effectiveness of serious gaming as a treatment complement. We question to what extent multidisciplinary rehabilitation with an additional serious gaming component is more effective than multidisciplinary rehabilitation without serious gaming for symptom reduction and clinically relevant improvement. Primarily, interdependent outcome domains of pain, fatigue, and emotional functioning (pain intensity, pain coping and cognition, fatigue complaints, and psychological distress) are studied, because they are considered to be relevant and plausible for the intervention and population [19, 78]. Secondary outcomes are patients' impression of overall improvement, general subjective health, and satisfaction with functioning and treatment.

Secondly, we aim to understand which innovation, patient, provider, and organization level factors influence the outcomes of serious gaming for patients. Innovation level factors could be design quality and compatibility with user routines. Patient level facilitators or barriers could be demographic, health status and intervention history factors. Serious gaming outcomes could also depend on complex provider behaviour by attitude, skill, and/or time constraints. Finally, outcomes of serious gaming could be influenced by its organization in a clinical setting. Therefore, we pose the question: what are the barriers and facilitators of outcome improvement through serious gaming according to patients, providers, and other stakeholders? Furthermore, we question how variation in serious gaming outcomes can be decomposed with plausible patient level differences and/or delivery conditions within the treatment setting (i.e., size of a debriefing group).

The third aim concerns *how* serious gaming contributes to patient outcomes. For this, we explore various serious gaming mechanisms, being the subjective experiences and objective performances in context that may affect health

outcomes. In addition, plausible linear effects between mechanisms and patient outcome variables are investigated. Achievement of all three research aims will inform the further development of a valid and practical programme theory of serious gaming outcomes in regular health care for patients with CP or FSS.

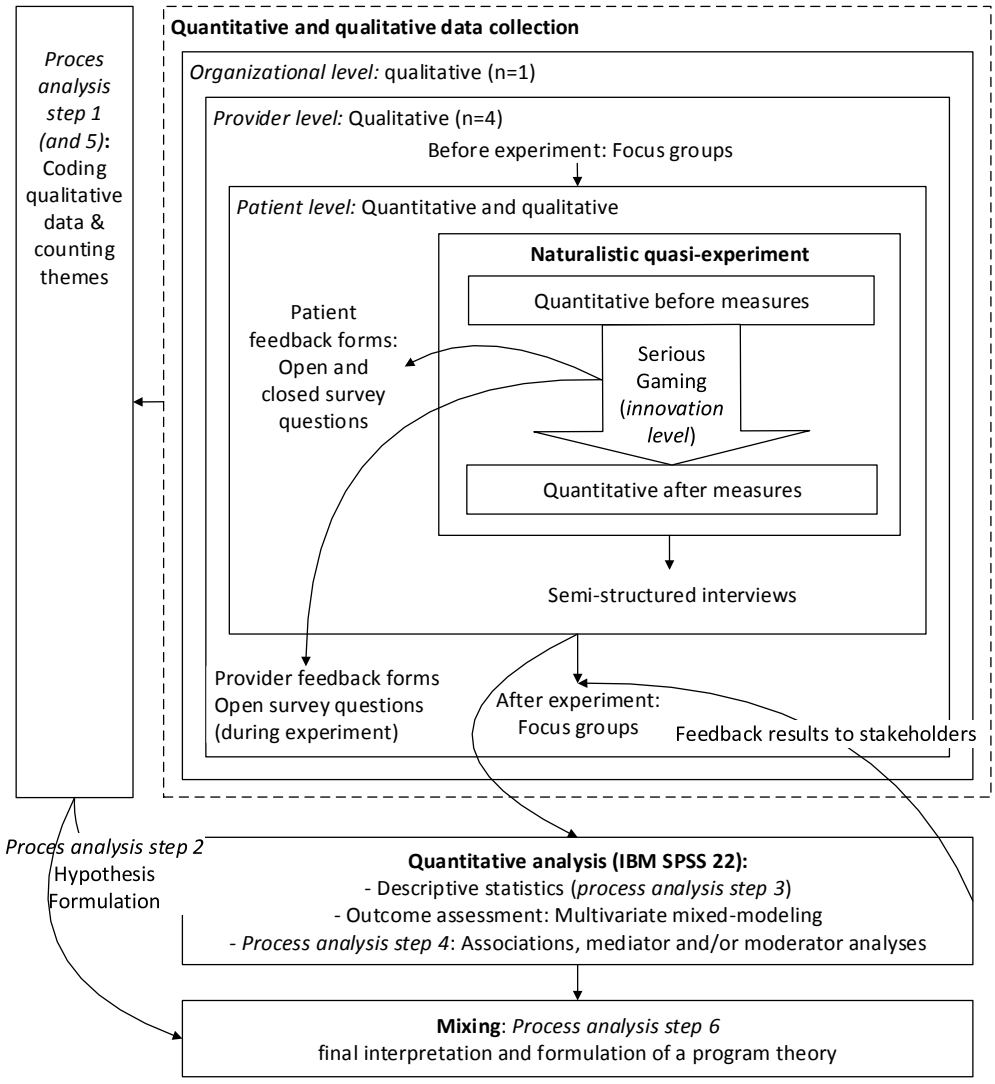
4.3 METHODS AND ANALYSES

4.3.1 Study design and procedure

An embedded experimental mixed-methods design is created by an integrated multidisciplinary research team (MV, HV, MJ, AZ, and AM) to address all three research aims in a single study (see Figure 1). For studying the first research aim, which is to estimate patient level outcome improvement due to serious gaming during regular outpatient rehabilitation, a two-armed naturalistic quasi-experiment is prioritized (displayed at the centre of Figure 1). A serious gaming intervention is deployed, for usage by all patients, at two sites of a Dutch outpatient rehabilitation clinic. Therefore, an intervention group is constituted of patients who receive the multidisciplinary rehabilitation programme with an additional serious gaming intervention. The control group consists of patients who simultaneously follow the same programme in two similar sites of the same clinic without serious gaming. Codified quantitative data from patient records will be retrieved and analysed to examine between group outcome differences. The protocol for the naturalistic quasi-experiment was entered in the Dutch trial register (NTR6020).

Embedding qualitative methods before, concurrently to, and after the quasi-experiment suits our second and third study aims. This mixed-method design is ideal for examining intervention processes, understanding mechanisms related to variables, and supporting programme theory development [252]. Herein, no intermediate qualitative results are communicated with providers and implementers during the experiment. Data collection started in April 2016 and is planned to end in March 2017, quantitative outcome data will be retrieved when concurrently collected qualitative data are analysed (February 2017).

Figure 1: Overview of the Mixed-Methods design



4.3.2 Recruitment

4.3.2.1 Sites and professionals

Two intervention sites where serious gaming is deployed participate in the study. For the recruitment of control subjects, two other sites (out of 18 sites as part of the same treatment centre) are selected based on similarity with regard to patient characteristics, facilities, protocols, history, personnel, location in or near a city in the southern Netherlands, and no other research projects planned during the

intervention period. The treatment centre provides rehabilitation care covered by health insurance in association with a university medical centre. Professional study participants are local stakeholders of serious gaming, including experts, implementers, and providers.

4.3.2.2 Patients

Patient candidates received an indication of eligibility for outpatient multidisciplinary rehabilitation from a rehabilitation physician, and completed half of their rehabilitation programme at a participating site. Physician indications of eligibility are followed, which are based on the results of diagnostic surveys, physical and psychological investigations, and clinical interviewing via teleconference. Accordingly, patient participant inclusion criteria are: being between 18 and 67 years of age, reporting the presence of pain for more than 6 months, or fatigue complaints or a musculoskeletal disease for more than 3 months, having no (more) indication for another (cost-) effective medical treatment, and have concomitant psychosocial problems. Patients are excluded from participation if: psychiatric symptoms are not adequately controlled, there is significant risk of psychological decompensation through a rehabilitation treatment, language or communication problems make it impossible to follow rehabilitation, and/or demonstrable inability to change behaviour (due to personality disorders, third party liabilities, or otherwise). An information letter, consent form, and verbal explanation are provided by local care providers. The recruitment process is monitored to ensure that all candidates are invited.

4.3.3 Interventions

4.3.3.1 Multidisciplinary rehabilitation programme

The outpatient multidisciplinary rehabilitation programme includes common bio-psychosocial approaches, and incorporates a focus on well-being and participation [184]. The standardized 16-week programme consists of on average 95 hours of individual or group sessions that are organized in modules and centrally assigned to individual patients based on diagnostic findings. Each patient is treated by a team of two physiotherapists and two registered master's degree psychologists. Psychotherapeutic techniques include Cognitive Behavioural Therapy and psychodynamic approaches. For all patients, treatment contains rationales, goal setting and feedback, social support, exposure treatment, behavioural repetition

and substitution, skills training (in relaxation, social skills, and meditation), and identity development techniques. Allocation of physical therapy, cognitive restructuring, eye movement desensitization, and an intensive 2-day well-being course depend on diagnostic findings for physical status, psychopathological symptoms [198], and fear avoidance beliefs [199], post-traumatic stress, and psychological well-being.

4.3.3.2 Serious gaming

4.3.3.2.1 Theory and change techniques of the serious game LAKA

Developer assumptions for the game LAKA have been documented throughout development and related to conceptual frameworks (see S2 Appendix, table 2.6) [42]. Serious gaming is proposed to promote practice for well-being improvement, and for identifying and diminishing distortions and biases of self. This may be helpful for patients with CP or FSS in reducing the burden of their symptoms [253]. Based on a review of information about the design rationale, functionality, validity proof (before outcome evaluation), and data protection measures of LAKA, an independent jury awarded 3 out of 5 attainable stars for quality (see S2 Appendix, table 2.7) [254].

The serious game LAKA promotes practice through an Avatar model. Before the game starts, participants are invited to identify with an Avatar of their chosen gender and name (Table 1). The storyline introduces an Avatar who recently experienced physical and social deterioration, senses an urgency to change, and engages in a trip around the world to learn about 'the art of living'. Player tasks are: to explore and select virtual action plans for 'encounters' with non-playing characters, to evaluate their 'satisfaction' about chosen actions, and to perform skills training in focused attention and open monitoring meditation exercises [40]. Encounter scenarios model uncertain events resulting in varying Avatar states depending on action plans chosen by players.

Table 1: Features, dose, and tasks

Features (frequency)	Tasks
Introduction (1)	Choose Avatar gender and name
	Receive instruction: to identify with the personal Avatar
	Introduction to Avatar storyline
	Receive task instructions from LAKA (non-playing character with a

	mentoring role)
Encounters (16): See S2 Appendix, Figure & table 2.2 for screenshots and user interface	Select action plans for the Avatar in encounters with non-playing characters (each instance offers 5 optional action plans, which are modelled after a reference set of values: generosity, moral discipline, patience, enthusiastic perseverance).
Mood scenarios (8)	Select action plans for the Avatar when subjected to an adverse event. Given the adverse scenario: think of what your own affective state would be in this situation, and bear in mind the depicted emotional state of the Avatar.
Reflections (4)	Assess satisfaction about selected Avatar actions on a scale of 0-10. Receive feedback from LAKA on chosen action plans. Receive feedback about the correspondence between satisfaction rating and LAKA assessment.
Attention training (3)	Guided (focused attention and open monitoring) meditation exercises for mental stability.
Tours (16)	Skip or listen to 'tour-guide' voiceovers informing about pictures of the location visited by the Avatar.
Loading screens	See where travel destinations are located on a geographical map.
Mini-games (8)	Action games: Steering a vehicle (by using tilt mechanism of tablet pc, or keyboard arrow controls) to arrive at the next encounter (reference: 'rocket bird'). Puzzle: Fix a road by connecting parts of the road to arrive at the next encounter (reference: 'plumber games').
Festive closing (1)	Replay of 'extreme' responses throughout the game.

Encounters are increasingly influenced by distant cultural meanings to challenge anticipation of the course of events (i.e., depending on the scenario, agreeable responding can result in a pleasant interaction or involvement in a scam). Players receive global feedback on the extent to which chosen actions correspond with a reference model for values. Self-reflective elements are interspersed with short casual action and puzzle games, images, and information associated with the location of the Avatar. These features are included to vary game play, and can be skipped.

4.3.3.2.2 Mode of delivery

In accordance with patient suggestions for optimal reach, the rehabilitation clinic delivers professional assistance and the occasion for playing the serious game LAKA on site, besides downloading and playing on a home computer [218]. Suitable rooms with Wi-Fi connection, tablet computers with LAKA installed, and headphones are provided. Four 1-hour sessions of serious gaming are planned for

1 to 6 patients simultaneously during weeks 9-12 of their rehabilitation programme. The sessions are scheduled in connection with other therapy sessions to ease coordination with daily activities. Staff members are available for consultation on accessing serious gaming (i.e., for technical issues and adaptation to special needs). Experienced therapists (1 physiotherapist, and 3 psychologists) facilitate the first session (introduce LAKA and instruct to complete the game independently during session 2 and 3) and the fourth session (debriefing). The goal of the debriefings was to discuss experiences of game play, technology acceptance and learning, and facilitate learning transfer to daily life. For external validity, no specific roles were assigned to other local stakeholders for the delivery of serious gaming (i.e., to observe 'natural' problem solving by implementers).

4.3.4 Programme theory

The framework of context, mechanism, outcome (CMO) configurations is used to structure ongoing development of a programme theory for serious gaming as a complement during multidisciplinary rehabilitation [255]. To illustrate, a patient with an active coping style self-exposed for a short amount of time to unsupported serious gaming during multidisciplinary rehabilitation (context), experienced enjoyment and discrepancy regarding valued self-identities (mechanism), and expected this to contribute to health improvement (outcome) [218]. Timely building blocks for CMO configurations for serious gaming are deduced from the literature. Besides by symptom categorization, serious gaming outcomes were interpreted by frameworks of rehabilitation mechanisms as self-improvements (see S2 Appendix, table 2.6) [19, 42, 78, 197, 253, 256]. Two comprehensive implementation models are used for the classification of context factors, such as planning and compatibility relative to other treatment components [257, 258]. Finally, mechanisms of serious gaming are discerned as gaming behaviours (frequency, length, and performance of game play), and user experiences of gaming, simulation, and information systems. More specifically, subjective mechanisms may involve sense of presence [259], technology acceptance [188], positive and negative affect [260], game-based learning [192], and perceived 'learning transfer' to daily life [251].

4.3.5 Measures

4.3.5.1 Quantitative data

Outcome and case-mix variables are retrieved from routinely administered clinical patient records after all participants have completed their rehabilitation programme. All patient variables are collected by the clinic through a standardized and secured web-surveying procedure, including facilitation of patients without convenient computer access and promotion of follow-up completion [218, 261], Outcomes are monitored at the indication of eligibility (at baseline), after 8 weeks of treatment (intermediate), and again after 16 weeks of treatment (post). Relevant and valid measures were available for assessing the primary outcomes (see Table 2)'. These endpoints include a numerical rating scale for current pain intensity [196], the pain coping and cognitions list (PCCL) [262], fatigue as assessed by the Checklist Individual Strength (CIS) [197], and psychopathological symptoms as measured by the Symptom Checklist (SCL-90) [198]. Secondary measures focus on clinical relevance, such as patients' global impression of improvement after treatment [78]. Another widely used single item Likert-scale rating is used for measuring general health (poor to excellent) [263].

Table 2: Quantitative outcome measures

Variables	Measures	Time of measurement
Primary outcomes		
Current pain intensity	1 item Numerical Rating Scale (NRS) 0-10	Baseline, intermediate, post treatment
Pain coping and cognition	Pain Coping and Cognitions List (PCCL)	
Fatigue	Checklist Individual Strength (CIS)	
Psychopathological symptoms	Symptom Check List (SCL-90)	
Secondary outcomes		
Clinically relevant improvement	Patient Global Impression of Change (PGIC)	Intermediate, post treatment
General subjective health	"What do you think of your current health in general?"	
Perceived functioning	"Please indicate how satisfied you are generally taken with your current level of functioning"	
Treatment satisfaction	Three Likert scale items, i.e. "Would you recommend this treatment centre to other rehabilitation patients?"	Post treatment only

Table 3: Patient characteristics

Variables	Variables (measurement)
Age	Years of age (calculated from registered date of birth)
Gender	% Female
Socio-economic status	Highest education level, source of income (categorical rating items)
Coping style	Utrecht Coping List (UCL) [264] (validated questionnaire)
Environment	Presence of problems with regard to social life, financial situation, trauma, work situation (categorical rating items)
Symptoms	Duration (months; calculated from the date of onset), course (categorical rating item), and pain location (standard physical examination report)
Physical status	Body Mass Index, blood pressure, musculoskeletal conditions (standard physical examination report)
Other treatment	(Changes of) presence of medication usage, frequency of health care visits, previous visits to health providers (medical specialists, physiotherapists, and/or psychologist) (categorical rating items).
Treatment (modules) received	Automatic logs of session presence (determined from absence registrations by health care providers)

Finally, numerical rating scale items are available to assess patients' satisfaction about treatment and functioning (see table 2). Patient variables are demographic, health status and treatment history information (see table 3). Intervention mechanisms may cover subjective experiences and objective behaviours of serious gaming (see table 4).

Automatic registrations in patient files enable objective assessment of serious gaming frequency, duration, progress, and performance. Moreover, a short survey was composed in collaboration with the rehabilitation centre to measure subjective experiences shortly after serious gaming. This survey contains items on perceptions of using a serious game (regarding usefulness, ease of use, trust, enjoyment, goal clarity, challenge, and learning [188, 192, 218]), the 10-item short form of the positive and negative affect scale [265], the involvement and realism scales from the I group Presence Questionnaire [259], and (0-10) numerical rating scale item on perceived learning transfer. A reminder was sent to intervention group participants if the survey was not completed within a week after their last gaming session. Finally, a questionnaire on patient values may be used to explore relationships between mechanisms and outcomes of serious gaming.

Table 4: Quantitative indicators for mechanisms

Variables	Measures	Respondents	Time of measure
Reach, dose, gaming performance	Data logs: frequency, timing, length, progress, and scores of play	Intervention group	During serious gaming (automatic)
Acceptability and playability	Selection of UTAUT2[1] items (perceived usefulness, ease of use, trust, enjoyment) Selection of EGameFlow items (clear goals, challenge, perceived learning)	Intervention group	Post serious gaming
Positive and negative affect	PANAS-SF[2]	Intervention group	Post serious gaming
Presence (general, involvement, and realism)	IGroup Sense of Presence Questionnaire item for general sense of presence, and subscales for involvement and realism.	Intervention group	Post serious gaming
Learning transfer	Numerical rating scale (0-10): "Use the following slider to indicate to what extent you expect that the LAKA sessions contribute to your daily life"	Intervention group	Post serious gaming
Values (expressed in thoughts and behaviour)	Values questionnaire[3]: 5-point Likert scales, i.e. "If I find it necessary, I'll intervene to help or to protect others".	Intervention and control groups	Baseline, intermediate, post treatment

[1] Unified theory of acceptance and use of technology

[2] Positive and negative affect scale – short form

[3] Psychometric properties are still under investigation. Empirical support for good scale internal consistency, and strong associations with psychological well-being in rehabilitating patients were documented in a report for the Dutch Committee on Test Affairs (COTAN).

4.3.5.2 Qualitative data

Protocols for focus group and semi-structured patient interviews are informed by the CMO building blocks and principles for interviewing in realist evaluation [266]. Accordingly, the interviewer starts with an open and explorative style, but may sometimes take an explanatory role to raise discussion about programme theory elements when CMO configurations become better delineated. Providers are expected to be especially knowledgeable about context and mechanisms of

serious gaming, while patients may say the most about context and outcomes. Purposive sampling of participants is used until reaching a point of data saturation. All interviews are tape-recorded and verbatim transcribed. Transcripts and a summary of findings are sent to participants by e-mail to enable them to check if their views are accurately reflected.

4.3.5.2.1 Stakeholder (focus group) interviewing

Four focus group interviews are held, two before and two after the naturalistic experiment, to involve stakeholders in the ongoing development of serious gaming and programme theory. Participant selection and topics are based on actual data needs. Heterogeneous groups of care providers, implementers, and experts (in ICT, well-being, and serious gaming) are invited for the first and last discussion meetings. The first interview focused on the research goals for an open discussion. The last group interview will focus on programme theory for member checking and refinement. Homogenous groups of provider participants may be invited for the second and third focus groups for more in-depth information. Provider participants are asked to share positive and/or negative feedback about serious gaming via a secured web-form. This includes information on the occurrence and management of adverse events and/or unintended effects during serious gaming.

4.3.5.2.2 Patient interviewing

Two open interview questions about gaming experience and perceived learning transfer are added to the post-gaming survey for intervention group participants. Patient participants with high and low scores on a 1-item numerical rating scale (0-10) for perceived learning transfer are invited for a semi-structured interview after their rehabilitation treatment. These interviewees are asked to describe their health outcomes during rehabilitation, and to list the three most important reasons why serious gaming did, or did not, contribute positively or negatively to this process. A point of saturation is reached if the three factors (context and/or mechanisms) mentioned are all richly described. Control group interviewees are matched to some of the intervention group interviewees to compare rehabilitation outcome changes for similar cases with versus without serious gaming.

4.3.6 Analysis

4.3.6.1 Statistical outcome evaluation

Quantitative data will be imported in SPSS 22, described after statistical inferences, and analysed on intention-to-treat basis. All case-mix variables are described for individual study participants, as well as the differences between intervention group and control group participants. Multivariate mixed-linear modelling techniques will be used to evaluate the extent to which serious gaming predicts variance in patient outcome levels between the intermediate and final outcome assessments of the rehabilitation programme. Effective sample size and intra-class coefficients will be calculated to determine dependency on hierarchical patterns in outcome variation by care provider levels. An optimal prediction model will be specified, correcting for potential unbalances between the study groups (at baseline and/or intermediate), and/or important higher-level random effects.

4.3.6.2 Process analyses

A programme theory will be created after a sequence of analysis steps. In each step, analyses will be performed completely by MV and in part by MJ or AZ (independent coding of interviews, and re-running syntax), and discussions will be held involving a third author (HV) to resolve differences and find agreement about the results. First, concurrently collected qualitative data analyses will be performed to identify plausible CMO configurations from the perspectives stakeholders. All qualitative data will be coded in vivo and higher order coded using CMO building blocks to determine configurations. Secondly, a selection of key CMO configurations will be made based on counts of the number of participants supporting them in their open text responses to the post-gaming survey. Hypotheses will contain specific expectations of (linear) relationships implied by the CMOs. If needed, additional provider or site level data (i.e., debriefing session group sizes) will be retrieved from clinical administration records. Third, quantitative data will be screened by testing internal consistency in SPSS or data triangulation with qualitative data if possible. Fourth, hypotheses will be tested with available and valid quantitative data. Fifth, data from the last focus group will be coded. Sixth, quantitative and qualitative findings will be mixed for an overall interpretation and drawing final conclusions.

4.3.6.3 Power calculation

From practical, theoretical and statistical perspectives, a powerful primary outcome assessment was anticipated by focusing on recruiting a sufficient number of individual patients from the four participating treatment facilities. The rehabilitation centre (n=1), intervention sites (n=2), as well as the number of time-points (3), are practically fixed. Analysis of unpublished pilot data suggested that variation in baseline to post treatment outcome changes between treatment locations might be negligible relative to individual variation within sites (intra-class correlations <.05).

G*Power was used for sample-size calculations [267]. A required sample size of 212 participants was calculated for determining a small to medium effect by means of a MANOVA test of global effects. Effect size estimation was based on meta-analysis results for the effects of serious games on cognition, motivation, and psychological outcomes [30]. The following parameters were inserted: for power (1-Beta)=0.8; effect-size f^2 (V)=.0625; type-II error probability (alpha)=.05; number of dependent variables=5; and number of groups=2. By the same standards, it was checked if the determined sample size would also be sufficient for independent univariate tests of variance on each of the primary outcomes.

Anticipating some level dependence and/or randomly missing data (pain coping and cognition measures are not filled out by patients reporting 0 pain intensity at baseline), 250 patient participants will be recruited. Assuming 20% treatment and study attrition rates and an average weekly inflow of 9 patients starting with their treatment within each of the four facilities, outcome data are available 6 months after recruiting the first patient.

4.3.7 Ethics and dissemination

Ethical approval for the mixed-methods protocol was obtained from the psychological ethics committee of Tilburg School of Social and Behavioural Sciences (EC-2016.25t). In the absence of a legal obligation for medical ethics review, independent judgement was provided on the protection of patient rights by conformity to the letter and rationale of the applicable laws and research practice. Patient participants are consented before participation, that is before receiving the additional (5-10 minute) survey (intervention group), being invited for a semi-structured interview, or retrieving their codified data. Participants were protected against harm by regular clinical safety measures throughout.

Professional participants are also consented before participation in qualitative data collections. Under supervision of MJ, MV is responsible for safe storage and the accessibility of (codified) research data to all authors. Qualitative and quantitative results will be presented and discussed together in one or more research article(s), and at one or more international scientific conferences. A summary of study results will be provided to the study participants.

4.4 DISCUSSION

The novelty of the serious gaming intervention and study methods are strengths of the proposed evaluation, but imply limitations as well. LAKA is the first serious game that promotes practice for self-process enhancement under highly prevalent adverse conditions such as CP or FSS. CMO configurations may be identified that are transferable to other populations and settings where similar approaches to behavioural change are beneficial [76]. However, internal and external validity are threatened due to divergence from the golden standard procedures of a (cluster) randomized controlled (multi-centre) trial. Instead, pragmatic considerations for the deployment of serious gaming during rehabilitation in two sites of a single Dutch centre led treatment allocation, recruitment, and data collection methods. Different comparisons with serious gaming (i.e., usual care, waiting list, or text based computer-based intervention), more elaborate diagnostic assessment, and outcome measurements including role participation and long-term follow-up are precluded. Still, conditional optimization of quasi-experimental methods is a legitimate strategy for obtaining evidence on the effectiveness of an intervention [48]. Apparent confounding factors (i.e., differences in usual treatment received) should be controlled for by appropriate methods. By the emergence of practical limitations, study strengths shift towards dealing with questions of process. The realist evaluation principles and mixed-methods used in this study are increasingly accepted in scientific communities as means to compensate for practical limitations and to build programme theories that enhance future predictions of intervention effects across patients and health care settings.

Legitimate application of mixed-methods is promoted by the protocol in various ways. First, participant recruitment and selection methods for quantitative and qualitative examinations allow a strong representation of patients receiving bio-psychosocial treatment in a regular outpatient setting. This differs from

studies in which the eligibility of applicants for computer-based intervention depends on motivation and/or ability to use a computer or internet facilities [119, 147]. Secondly, perspectives of insiders (patients, health care providers and developers) and outsiders (independent experts and members of the research team) will be utilized. Third, relevant theoretical constructs are specified before quantitative and qualitative data collections to prevent process analysis results being strongly affected by the sequencing of qualitative and quantitative methods. Fourth, predefined steps structure data convergence and switches in epistemological paradigms when qualitative methods are used to propose quantitative results (in advance) and to explain them (afterwards).

Abbreviations:

- **CMO:** Context, mechanism, outcome
- **CP:** Chronic pain
- **FSS:** Functional somatic syndrome

5 OUTCOME EVALUATION

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Title: Effectiveness of serious gaming During Multidisciplinary Rehabilitation for Patients with Complex Chronic Pain or Fatigue: A Natural Quasi-experiment

5.1 ABSTRACT

Background: Current evidence for the effectiveness of specialist multidisciplinary programmes for burdensome chronic pain and functional somatic syndromes drives the effort to improve approaches, strategies, and delivery modes. It remains unknown to what extent and in what respect serious gaming during the regular outpatient rehabilitation can contribute to health outcomes.

Objective: The objectives of our study were to determine the effect of additional serious gaming on (1) physical and emotional functioning in general; (2) particular outcome domains; and (3) patient global impressions of change, general health, and functioning and to determine (4) the dependency of serious gaming effects on adherence.

Methods: We conducted a naturalistic quasi-experiment using embedded qualitative methods. The intervention group patients received an additional guided (mindfulness-based) serious gaming intervention during weeks 9-12 of a 16-week rehabilitation programme at 2 sites of a Dutch rehabilitation clinic. Simultaneously, 119 control group patients followed the same programme without serious gaming at 2 similar sites of the same clinic. Data consisted of 10 semi structured patient interviews and routinely collected patient self-reported outcomes. First, multivariate linear mixed modelling was used to simultaneously estimate a group effect on the outcome change between weeks 8 and 16 in 4 primary outcomes: current pain intensity, fatigue, pain catastrophizing, and psychological distress. Second, similar univariate linear mixed models were used to estimate effects on particular (unstandardized) outcomes. Third, secondary outcomes (i.e., global impression of change, general health, functioning, and treatment satisfaction) were compared between the groups using independent t tests. Finally, subgroups were established according to the levels of adherence using log data. Influences of observed confounding factors were considered throughout analyses.

Results: Of 329 eligible patients, 156 intervention group and 119 control group patients (N=275) with mostly chronic back pain and concomitant psychosocial problems participated in this study. Of all, 119 patients played ≥75% of the game. First, the standardized means across the 4 primary outcomes showed a

significantly more favourable degree of change during the second part of the treatment for the intervention group than for the control group (beta=−0.119, SE=0.046, P=.009). Second, the intervention group showed a greater outcome change in depressive mood (b=−2.748, SE=1.072, P=.011) but not in "insufficiency" or concentration problems. Third, no significant group effects on secondary outcomes were found. Fourth, adherence was generally high and invariant.

Conclusions: The findings of this study suggest a very small favourable average effect on relevant health outcomes of additional serious gaming during multidisciplinary rehabilitation. The indication that serious gaming could be a relatively time-efficient component warrants further research into if, when, how, and for which patients serious gaming could be cost-effective in treatment and why.

Trial Registration: Netherlands Trial Registry NTR6020; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=6020 (Archived by WebCite at http://www.webcitation.org/71IIoTXkj)

5.2 INTRODUCTION

5.2.1 Background

In a European survey, it was estimated that 77% of patients with chronic pain (CP) do not access specialist treatments and 40% cannot effectively control their pain [9]. CP is defined by the presence of pain beyond a usual 3- to 6-month duration of organic recovery that may, but does not have to, have an organic cause [9]. Functional somatic syndromes (FSS) are characterized by a persistent pattern of bodily symptoms (i.e., pain, fatigue, tinnitus, bowel complaints, and palpitations) for which adequate examination does not reveal sufficiently explanatory specified pathology [8]. Both classifications include, among others, fibromyalgia, chronic low back pain, and irritable bowel syndromes. Global prevalence estimates vary with location and case criteria (severity and disability) and are generally considered high (7%-64% for CP, 3%-43% for tinnitus, 14%-33% for non-cardiac chest pain, and 1% for chronic fatigue syndrome) [58, 220, 233, 268-271]. In the absence of satisfactory biomedical solutions, biopsychosocial interventions are offered for improving the physical and emotional functioning [8, 9]. A major challenge is to identify which behaviour change intervention approaches [272], techniques [104], and delivery modes (e.g., computer based) are most accessible and (cost-)effective for certain patients in certain health care settings [18, 60]. Herein, a contribution may be made by the pragmatic effectiveness evaluation of a serious gaming intervention (i.e., LAKA) during multidisciplinary rehabilitation for patients with emotional or role dysfunctions in association with CP or fatigue [273]. It is hitherto unknown whether, to what extent, and in what respect serious games complement other treatment modes in facilitating intervention effects that are meaningful for patients when offered in addition to other modes of treatment as in regular outpatient multidisciplinary rehabilitation.

5.2.2 Existing treatment gaps

National and international guidelines consider various behavioural interventions to be evidence based, but they change with developing insights into the various CP or FSS conditions [52, 274]. Intensive multidisciplinary rehabilitation programmes are indicated if locally accessible and (unimodal) conservative medication, minimal self-guided intervention, and physical and psychological therapy do not suffice [8, 14, 233, 274]. Ideally, treatment plans are tailored to individual symptom patterns through interdisciplinary procedures Supporting

evidence from randomized controlled trials (RCTs) consists of, at most, medium-sized effects for biopsychosocial interventions compared with alternative treatments [14, 233]. An improvement is sought in the modest additional effects of the multi- or interdisciplinary rehabilitation over other kinds of "unimodal" treatments [14, 26, 233, 275]. There's growing evidence for the efficacy of acceptance- and mindfulness-based interventions, which can be included in the multi- or interdisciplinary rehabilitation [233, 272]. Rather than addressing certain presumed maladaptive illness beliefs, this sort of approach aims to cultivate self-awareness, self-regulation, and self-transcendence in response to aversive conditions such as CP or FSS [42, 272]. Moreover, behavioural interventions have approximately equivalent effects when delivered via computers or internet, but adherence to such interventions can be disappointing [60, 159]. Promotion of motivation and adherence (by professionals) may lead to better therapy outcomes [276] and is likely to be of help to patients when using computer-based programmes [159]. Few trials have reported mixed results for the efficacy of varied computer-delivered interventions (i.e., mobile phone, automated telephone responding, and online support group) offered in addition to face-to-face intervention to patients with CP [55, 134, 141]. Generally, effect studies of biopsychosocial interventions may need to improve in their methodological quality (i.e., statistical power, risk of selection and reporting bias) and uniformity (i.e., definitions of case and recovery, diagnostic methods, subjective and objective outcome criteria, and programme description) [277, 278].

5.2.3 Why serious games may offer a potential Solution

Serious games, which primarily aim at health benefits, may take the form of a video game [30]. Indeed, how harmful or conducive video gaming is for behaviour and health depends on the content (e.g., whether it reinforces aggressive or prosocial actions) and context (i.e., players and instructional support) of the game [217, 250]. Serious games may combine small behavioural and clinical benefits with independent accessibility and standardized content of computer-based interventions as well as unique qualities for learning such as intrinsic motivation, enjoyment, positive affect, sense of presence, and meta-cognition [30, 43, 94, 242]. Games are a ubiquitous but undefinable cultural phenomenon described as bounded "spaces" physically, imaginarily, or in time apart from ongoing reality, wherein individuals involve voluntarily, create meanings, and develop adaptive

capacities, such as sports and rituals [279, 280]. Intrinsic motivation, as in games, is beneficial for learning quality [281]. It has been hypothesized that behavioural change is strengthened by engagement qualities triggered by storytelling, fantasy, and interactivity in serious games [242]. In the fields of mental health care and rehabilitation, gaming, motion capturing, and virtual reality technologies potentially support the treatment of various well-known conditions such as depression, anxiety, phobias, post stroke, and acute pain [44, 179, 180, 237, 240, 251, 282]. After serious gaming, debriefing may be offered to facilitate the transfer of patient experiences into targeted individual learning results [251]. Thus, previous studies have shared the idea of (subtle) positive moderation of treatment effects because of distinctive beneficial motivational qualities triggered by features of serious games. However, adequately powered studies on the comparative effects of games for health are lacking in general, and little to nothing is known about their complementary effectiveness in regular health care contexts, such as multidisciplinary rehabilitation [44]. Moreover, patient adherence to serious gaming when deployed in practice and its influence on outcomes require empirical assessment in effectiveness evaluation [47].

5.2.4 A mindfulness approach to serious gaming in multidisciplinary rehabilitation

Serious gaming can be a complementary modality that strengthens mindfulness-based modules in treatments like multidisciplinary rehabilitation. Adopting a mindfulness approach to serious gaming deviates from an approach wherein particular antecedent cognitions of health behaviours are targeted [242]. Mindfulness approaches offer mental training principles (i.e., focused attention, open monitoring, or ethical enhancement) for promoting (1) a temporary state of non-judgmental, nonreactive, present-centred attention and awareness (self-awareness); (2) a capacity to effectively modulate behaviour (self-regulation); and (3) a positive relationship between self and others, transcending self-focused needs and increasing prosocial characteristics (self-transcendence) [42]. A complementary role of mindfulness-based serious gaming might not necessarily be to facilitate mental training in patients over prolonged periods, but rather to promote independent practicing by any (other) means in the context of daily life. Plausibly, mental training objectives can be temporarily achieved in conjunction with gaming, but it can contradict an obsessive drive that could characterize long-

term and frequent video gaming [245, 283]. Over longer durations, individuals may apply mental training principles independently in various ways, depending on behavioural factors (recollection of instructions, intent, habit) [42]. Change techniques (e.g., commitment to change, action planning, drawing attention to discrepancies between behaviour and goals, non-contingent praise, performance instructions, self-monitoring, and salient feedback on behaviour) as well as emotional and social consequences, reduction of negative emotions, values affirmation, etc. [104] for (novice) mental training activities could be integrated (via an "Avatar" role) into a serious game. From this line of argument, it was proposed that a short serious gaming intervention adds to the effectiveness of a mindfulness-based approach during multidisciplinary rehabilitation for (subtly) better effects on relevant health outcomes in patients with CP or FSS.

5.2.5 Objectives

In this study, we investigated the effectiveness of serious gaming as a complement to the multidisciplinary rehabilitation of patients with CP or FSS. The selection of health outcomes was guided by a field consensus on the relevance of physical and emotional functioning, patients' global impression of improvement, and negative effect [78]. The primary objective was to determine the effect of additional serious gaming on multiple domains of physical and emotional functioning simultaneously. Secondary objectives were to understand which outcome domains are particularly affected, positively or negatively, by serious gaming during rehabilitation and whether serious gaming affects patient's global impressions of change, general health, and functioning. The final objective was to determine whether outcomes of serious gaming are dependent on adherence. Adherence is defined as the extent to which patients expose themselves, in terms of content, frequency, and duration, to the "hard core" of a serious gaming intervention—playing a serious game and attend the debriefing. The following were the research questions:

1. To what extent does an additional serious gaming intervention affect a change in patients' physical and emotional functioning during regular multidisciplinary rehabilitation?
2. Regarding which particular domain(s) of physical and emotional functioning does an additional serious gaming intervention affect outcome change during multidisciplinary rehabilitation?

3. To what extent does an additional serious gaming intervention during multidisciplinary rehabilitation affect patients' impressions of change, subjective health and functioning, and satisfaction with treatment?
4. To what extent is the degree of effectiveness dependent on levels of adherence?

5.3 METHODS

5.3.1 Study design

A protocol for this embedded experimental mixed-methods study was registered (preresults) in the Dutch trial register (NTR6020), previously published in detail [273], and followed accordingly. General information and important executive details relevant to the present objectives are discussed here. In the absence of a legal obligation for medical ethics review, the protocol was reviewed for the protection of patients' rights in accordance with the letter and reasoning of applicable legislation and research practice and endorsed by the Psychological Ethics Committee of the Tilburg School of Social Sciences (EC-2016.25t). The study design sorts with the nature of multidisciplinary rehabilitation, which is complicated by tailoring, multiple interacting components, and outcome multidimensionality [47]. Quantitative methods were prioritized for assessment purposes. The two-armed naturalistic quasi-experiment was set up pragmatically, comprising an intervention group of patients who received an additional serious gaming intervention offered during weeks 9-12 of a standardized 16-week rehabilitation programme at 2 sites of a Dutch rehabilitation clinic. Simultaneously, an approximately equal number of control group patients followed the same programme without serious gaming, as usual, at 2 similar sites of the same clinic (from February 2016 to January 2017). Concurrently collected qualitative data were first used to refine hypotheses blind to trial outcomes, and later for triangulation and post hoc explanation of quantitative results.

5.3.2 Setting, recruitment, and data sources

The convenient selection of control sites aimed for homogeneity across the study groups. The 4 participating sites were located in the south of the Netherlands, where multidisciplinary biopsychosocial rehabilitation, but not serious gaming, is covered under basic health care insurance. In view of ecological validity, all patients with a regular physician indication for multidisciplinary rehabilitation who

completed the first 8 weeks of rehabilitation were considered eligible for this study. From the beginning of the second half of their rehabilitation programme (July-November 2016), patients were consented by their direct care providers. This timing was chosen for patient convenience and optimal response. To lower the risk of selection bias, patient recruitment was closely monitored through regular site visits. Consent was requested for the processing of patients' codified clinical diagnostic and outcome data and, perhaps, being contacted for an interview. Outcome data consisted of patients' routine outcome monitoring administered by the clinic through a standardized Web-surveying procedure at the baseline (t0), intermediate (t1: after 8 weeks of treatment), and posttreatment (t2: after 16 weeks of treatment). Only intervention group candidates were requested to answer feedback questions through the same familiar Web-survey procedure immediately after their debriefing session.

To avoid bias by inflicting outcome expectations in patients as subjects and outcomes assessors, information letters did not contain statements about presumed effects of serious gaming or parallel group comparison. After serious gaming, feedback data were made available to the researchers to support the concurrent qualitative research, but routinely collected clinical (diagnostic and outcome) data were not. In this way, data management served to prevent the risk of biased interpretation through breaching the protocoled sequence of hypotheses refinement and quantitative testing.

5.3.3 Patients

Based on physical and psychological examination results and clinical interviews, physicians indicated eligibility for multidisciplinary rehabilitation treatment based on the following inclusion criteria. The eligible patients were between 18-67 years of age, had pain for more than 6 months or fatigue complaints or musculoskeletal disease for more than 3 months, had no indication for another more cost-effective treatment, and had concomitant psychosocial problems. The exclusion criteria were as follows: patients with psychiatric symptoms that are not adequately controlled, a marked risk of psychological decompensation through a rehabilitation treatment, language or communication problems that make it impossible to follow rehabilitation, or demonstrable inability to change behaviour (e.g., due to personality disorders, third party liabilities, or otherwise). Notably, no additional computer literacy criteria were applied for participation in this study.

5.3.4 Interventions

Both study groups received an intensive 16-week biopsychosocial multidisciplinary rehabilitation programme with a particular focus on well-being and social role participation (see Table 1) [184].

Table 1: Overview of programme components offered during first and second half of the regular multidisciplinary rehabilitation programme

Component	Weeks 1-8	Weeks 9-16
Physical therapy	• Graded activity (group) • Exercise therapy • Physiotherapy[1] • Education (lifestyle, pain physiology)	• Graded activity (group) • Exercise therapy
Psychotherapy approaches	• Coping with stress • Extinction of fear-avoidance beliefs[1] • Cognitive restructuring[1] • Eye movement desensitization[1] • Mentalisation techniques[1]	• Coping with stress • Cognitive restructuring
Activating and counselling in social role participation	• Work and health (education and counselling) • Social skills	
Mindfulness interventions	• Rationale • Psychological well-being assessment • Mental training	Mental training
	Additional 2-day course (mental training skills)	

[1]Allocation dependent on examination results.

Under the supervision of a rehabilitation physician, patients received on average 100 hours of treatment in either one-on-one or in group settings from a team of 2 physiotherapists and 2 registered psychologists with a master's degree. Weekly intensity varied between 3 and 7 hours, decreasing with an increase in social role participation throughout the programme. Overall, patients received 38% physiotherapy, 30% mindfulness approaches, 23% (other kinds of) psychotherapy, and 9% of activating and counselling in social role participation The various interventions were centrally assigned, based on individual examination results for physical status, psychological and posttraumatic distress, coping, cognition, and well-being. In this study, the strategies used to promote health behaviour were as

follows: shaping knowledge about antecedents and health consequences, goal setting and feedback, social support, exposure, behavioural repetition and substitution, skills training (in relaxation, social skills, and mental training), and identity development (i.e., cognitive restructuring and values affirmation). Mindfulness interventions already included in the basic programme included basic rationales, mental training instructions, and psychological well-being assessment. An intensive 2-day mental training course was offered to all patients, except those with high levels of well-being.

The treatment offered to the intervention group only differed systematically from the control group in the addition of a serious gaming module (the control group did not receive something else instead); this was verified empirically. For the intervention group, the rehabilitation clinic had suitable facilitated rooms with Wi-Fi connections, tablet PCs installed with the serious game "LAKA," and the automated planning of four 1-hour small group sessions (1-6 patients simultaneously) in connection to regular therapy hours (mostly exercise sessions at the beginning or end of a working day) during weeks 9-12. Sessions were planned for patients to have sufficient time for completing the game, at least, once. Patients logged in with their personal identification number and self-chosen password with which they also accessed Web surveys. Experienced therapists (3 psychologists and 1 physiotherapist) were scheduled to provide support during the first (introduction) and fourth (debriefing) sessions. The goal of debriefings was to discuss the experiences of game play and technology acceptance and to transfer learning results to patients' daily lives. Other local staff members managed the accessibility of the game LAKA during sessions 2 and 3. Notably, patients could also download and play LAKA at home. Local therapists and other staff participated in developing their role in the delivery of serious gaming.

5.3.4.1 The serious game LAKA

The serious game LAKA is an adventure game where patients take the role of an Avatar during a virtual trip around the world. The game is easy to control using a touch-screen tablet computer and takes on average 2.5 hours to complete (see S2 Appendix Figure 2.2 for screenshots).

In LAKA, patient players perform alternate tasks vicariously; they select optional responses in various encounters with other characters, monitor and

evaluate satisfaction about selected responses (and their consequences), and meditate (3-minute exercises). First, players select between a male or female Avatar and assign a name. It was prompted that Avatar choices reflect those of the player. A cut-scene sets up the story; the Avatar, who wants change after experiencing a deterioration in physical and social functioning, meets a non-paying character (NPC) named LAKA. LAKA challenges the Avatar to make "conscious" decisions during 16 "encounters" with other NPCs, for example, when standing in line, on getting invited to someone's home, and at 4 destinations (i.e., London, Turkey, Asia, and Africa) on a trip around the world. Each "encounter" is built as a flow of Avatar actions and NPC responses.

For each Avatar action, 1 of 5 options (e.g., physically interact, verbally react, or ignore something) can be preselected and confirmed by players. These options are modelled after a set of reference values—generosity, moral discipline, forbearance, and enthusiastic perseverance. NPC responses are unpredictable, for example, a friendly act can result in a kind response or being scammed. At the end of each destination, LAKA asks the Avatar to self-rate the level of "satisfaction" regarding his or her choices. Indirect feedback, in the form of a number of puzzle pieces, is given by (1) the degree of correspondence of Avatar choices with the reference values and (2) the degree to which that correspondence agrees with satisfaction ratings. When the Avatar is depicted "mind-wandering" when traveling across destinations, instructions are received for a basic meditation exercise (focused attention and open monitoring) [40]. These model-based elements are interspersed with short action games, puzzle games, images, and information associated with the location of the Avatar to be enjoyed or skipped by preference.

5.3.5 Quantitative measures

5.3.5.1 Outcomes

Table 2 provides an overview of the outcome variables, surveys with references to instrument validity information, and times of assessment. Available primary outcome measures for operationalizing elements of research questions 1 and 2 included 4 evidently valid numerical rating- and Likert-scale measures that operationalize relevant and plausible targets for mindfulness-based intervention in the target group [78, 272]: a numerical rating scale for the current pain intensity, the Checklist Individual Strength (CIS) for fatigue, the catastrophizing

subscale of the pain coping and cognitions list, and the Symptoms Checklist (SCL-90) for psychological distress [196-198, 262].

Table 2. Primary and secondary outcome measures.

Variables	Survey information	Time[1]
Primary outcomes		
Pain intensity	Current pain intensity Numerical Rating Scale (NRS) 0-100 [53]	t0, t1, t2
Fatigue	Checklist Individual Strength (CIS)[197]	t0, t1, t2
Psychological distress	Symptom Check List (SCL-90)[198]	t0, t1, t2
Pain coping & cognition	Pain Coping & Cognitions List; catastrophizing subscale (PCCL)[262]	t0, t1, t2
Secondary outcomes		
Global impression of change, general health, and functioning	• How do you assess your health, compared to the situation at the start of your treatment? (-2; much, or -1; slightly declined, 0; neither declined nor improved, 1; slightly, or 2; much improved) • What do you think of your current health in general? (0; bad – 100; excellent) • Please indicate how satisfied you are generally taken with your current level of functioning. (0; not at all satisfied - 100; very satisfied) • Please indicate the distance from your "old" level of functioning before the onset of the complaint. (0; very far removed – 100 not at all removed)	t1, t2
Treatment satisfaction	• Would you recommend this treatment centre to other rehabilitation patients? (1; certainly not, 2; probably not, 3; probably yes, 4; certainly yes); item from the consumer quality (CQ) index [284] • Which grade would you give to the rehabilitation centre? (0-10) (CQ-index) • Did the treatment meet your expectations? (1; not at all, 2; mostly not, 3; mostly, 4; completely)	t2

[1]t0=baseline measurement, t1=measured at intermediate (after 8 weeks of treatment), t2=measured post treatment (after 16 weeks of treatment).

In addition, Likert-scale items on patients' global impression of change (PGIC), general health and functioning, and treatment satisfaction were available to operationalize secondary outcomes. The PGIC was measured using a single ordinal scale item [78]. Three available 0-100 numerically scaled questionnaire items about perceived health and functioning formed an internally consistent scale

(Cronbach alpha at t1=.80, at t2=.75) for general subjective health and functioning. Furthermore, 3 different questions assessed the treatment satisfaction, 2 of which were taken from the consumer quality index for rehabilitation centres [284].

5.3.5.2 Adherence

The operationalization of adherence distinguishes between progress in game play and debriefing attendance. The latter was established from clinical recordings of presence at either the initially planned or a rescheduled debriefing session. Log data from the game, designed to track the progress and give feedback on the performance, were used to determine the categories of completion percentage. These categories (5-1) represent 0%-6% completion when no progression logs were observed and 100% game completion when patients played the game LAKA more than once.

5.3.5.3 Case description and potential confounders

Data retrieved for describing patients and enabling the optimal control for observed confounding factors consist of demographics, medical history, physical and psychological examination results, and registrations of allocated and attended interventions.

5.3.6 Study size

Study size was determined by a priori power calculation as described in detail in the protocol [273]. G*Power was used to calculate a required sample size of 212 patients. These calculations were based on a multivariate analysis of variance of global effects (1−beta=0.8, f 2 =0.0625, alpha=.05, 2 groups, and maximally 5 outcomes). By taking a margin of 20% for dropout and missing values into account, the minimum number of patients was finally determined at 250.

5.3.7 Statistical methods

All statistical analyses were performed using SPSS 22 (IBM, New York). Descriptive statistics and chi-square and Student t tests were used to summarize demographic, disease-specific, treatment exposure, and baseline outcome characteristics. Variables that may differ per group on the baseline were added as covariates in subsequent analyses. Statistical methods were generally aimed at

testing two-sided hypotheses regarding study group differences in differences between intermediate and posttreatment outcome levels as this corresponds with the timing of the additional serious gaming intervention. Furthermore, Sidak-Holm correction was used when controlling for multiple outcome testing [285].

First, a multivariate mixed linear effect model was fitted to estimate a parameter for the study group difference in simultaneous change of the 4 primary outcomes between intermediate and post treatment assessments. For this, the MIXED procedure for defining parallel growth processes was applied on standardized scores of the 4 primary outcome variables (Textbox 1) [286].

Textbox 1. Linear mixed modelling operations

Operational details on the (planned or initial) multivariate linear mixed model:

- All models applied the restricted maximum likelihood estimation.
- MIXED requires a vertical (re)structured dataset with all outcome values inserted in one column, nesting primary outcomes (4) and time factors (3) within individuals.
- Indexes were created for individuals (1-275), outcomes over time (1-12), outcomes (pain intensity=1, fatigue=2, catastrophizing=3, and psychological distress=4), time (baseline=1, post=2, and intermediate=3 [reference category]), and group (1=intervention, and 2=control [reference category]).
- The procedure used standardized outcome values, calculated separately within outcomes.
- An unstructured covariance matrix (UN) for the random effects and a heterogeneous autoregressive matrix for the repeated effects were assumed when fitting multivariate models. Use of alternative covariance structures (UN, compound symmetry, autoregressive, Toeplitz, and ante dependent) either disabled convergence or resulted in worse fit.
- Basic model specification: the outcome index was specified as randomly varying for the estimation of intercepts for each of the 4 outcomes. The planned “basic” model contained 11 fixed-effect parameters, including 4 outcome factors, 3 treatment sites, 2 time factors (1=intermediate vs baseline, 2=intermediate vs post), and 2 group × time factors (group × time 1, group × time 2), with random error terms (10) and repeated effects (13), adding up to 34 parameters to be estimated in total.
- Model fit changes, that is, exclusions (i.e., site and time factors) or inclusions (covariates), were assessed using (chi-square) tests for differences in the −2 Log Likelihood information criterion.
- Sensitivity analyses revealing similar results included multivariate models run on full cases only, outcome data after outlier removal (z-scores above 3 or 5), and alternative z-score calculations.

Operational details for univariate mixed linear models:

- An unstructured covariance matrix was assumed for all univariate models.
- Univariate models included the same covariates as the multivariate models.

The procedure facilitates an intention-to-treat analysis, optimizes statistical power, imposes an equality constraint on parameter estimates across multiple

outcome measures, and takes outcome interdependencies into account. Hereby, the parameter estimation is unbiased under the assumption of missing data at random. To correct the parameter estimate for design limitations, it was modelled together with components that are not logically attributable to the serious gaming intervention, including global time and group effects, group differences in outcome changes in time prior to serious gaming, and covariates. Furthermore, selections between nested models, which is, excluding or including factors for time, treatment sites, and covariates were based on the statistical significance of changes in the model fit.

Subsequently, reliable change indexes (RCIs) were calculated (again based solely on the difference between intermediate and posttreatment scores) to determine within-group proportions of individual patients who reported improvement (RC>1.96) or decline (RCI>1.96) [287]. Improvement was defined as a clinically significant decrease (RCI<-1.96) in one or more of the 4 primary outcome variables. Decline was defined as a reliable increase in one or more outcomes (RCI>1.96) When patients did not show decline or improvement, their status was deemed stable. Differences in proportions in these categories were compared between the groups.
Second, effects of serious gaming on particular plausible outcome types identified through qualitative research were estimated using univariate mixed linear effect models of unstandardized outcomes. Third, (changes in) secondary outcomes were compared between the groups. Fourth, the multivariate linear mixed model was rerun after replacing the original group dummy variable by ordinal adherence variables to calculate parameter estimates separately for subgroups of differing rates of serious gaming progress and debriefing the attendance relative to controls (the reference category).

5.3.8 Concurrent qualitative methods

Qualitative data consisted of patients' typed responses to an open feedback question and audio recorded, verbatim transcribed semi structured interviews. The open feedback question was: "How do you think serious gaming will contribute to your daily life (ranging from 0=negatively or nothing to 10=hugely)? And in what way?" We purposively selected 8 patients with varying expected contributions of serious gaming for semi structured face-to-face interviews

(lasting 30-60 minutes). Of them, 2 were selected for their high expectations (scoring ≥9), 2 for their low expectations (scoring ≤1), and 4 for their mediocre expectations (4-6) regarding the contribution of serious gaming to their daily living. In addition, telephone interviews were planned with control group subjects who had been matched by direct care providers on case descriptions by gender, age, symptom patterns, and coping style. However, this was stopped after 2 short interviews (lasting <15 minutes) as it was not regarded informative due to case differences beyond the small set of matching variables. All interviews started with a request to patients to talk openly about their health status before rehabilitation and any changes experienced throughout. Subsequently, patients were invited to elaborate on the perceived contribution of serious gaming.

A deductive content analysis approach was performed on the interview transcripts using Atlas.ti. The first 4 interviews were coded independently by MV and a second author (MJ or AZ). Then, because no more differences in coding were observed, MV coded the remaining interviews. First, data were reduced by distinguishing text fragments related to patients' expected health outcomes. To those fragments, labels were attached according to sensitizing concepts about (subjective) health outcomes because existing theoretical frameworks on relevant health outcome dimensions were available and preselected for quantitative operationalisations [196-198, 262]. Those sensitizing concepts covered relevant outcome domains for patients with CP (physical symptoms, physical functioning, and emotional functioning (e.g., anxiety and depressed mood) [198] or fatigue (subjective fatigue and motivation and concentration problems) [197].

5.4 RESULTS

5.4.1 Participants

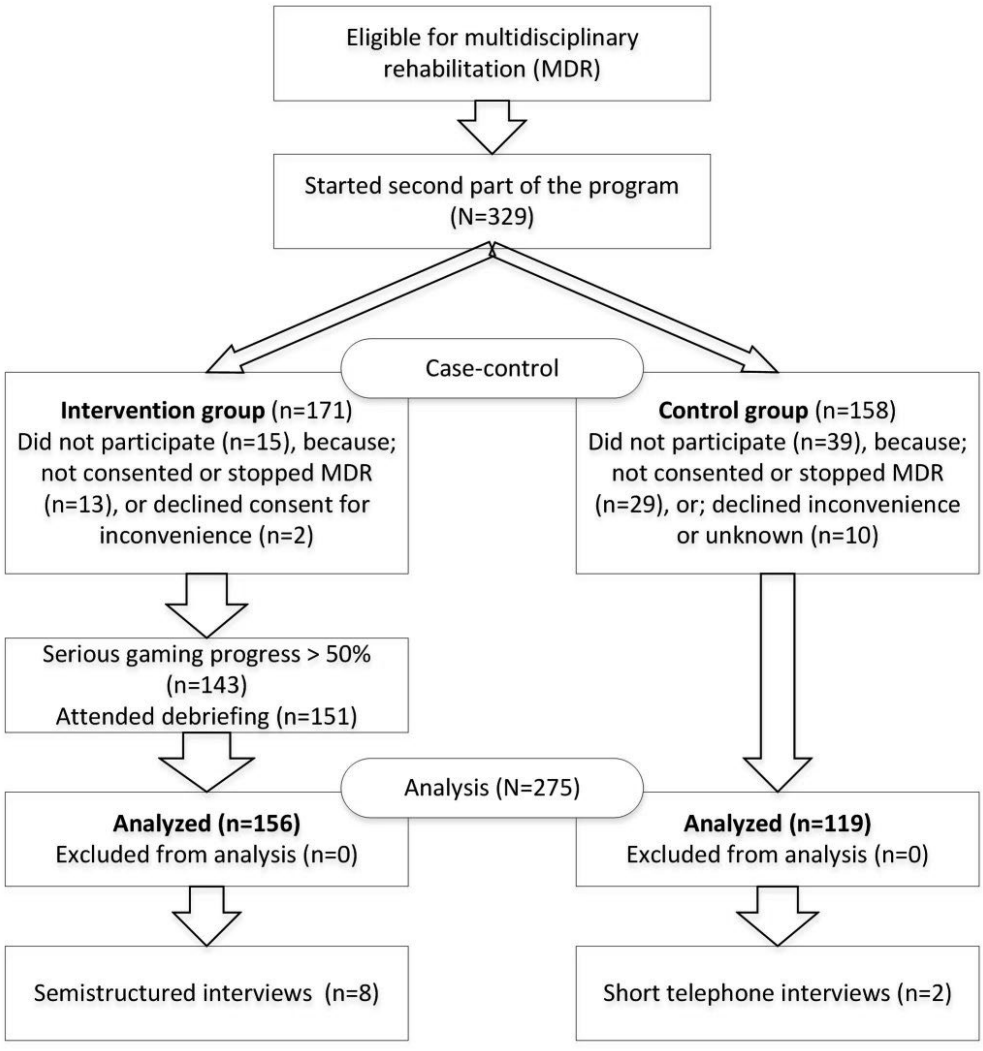
Recruitment was stopped when sufficient numbers of participants were included in both study groups. By then, 83.6% (275/329) of eligible patients who had started the second part of the treatment consented to participate—156 in the intervention and 119 in the control group (Figure 1). A decline in participation due to reasons such as inconvenience (i.e., presumed burdens of the treatment or study at the time of consent), delayed consent, and thereby missing patients who stopped participating during the second part of the treatment was observed more

often at control sites. Furthermore, posttreatment data were missing for 1 control group patient and 7 intervention group patients.

5.4.2 Descriptive data

Back pain was the most prevalent physical symptom reported (184/275, 66.9%), but pain symptoms with other origins (headaches, gastrointestinal, fibromyalgia, and osteoarthritis) were reported as well (Table 3).

Figure 1. CONSORT flow diagram of participants



n=number of patients, MDR=Multidisciplinary rehabilitation

Social problems were also prominent, with 49.8% (137/275) of the patients experiencing problems with family members. The modal norm group categories for the SCL-90 anxiety and depression symptom scales were “very high” relative to “healthy individuals” and “high” relative to patients with CP, but “below average” relative to psychiatric patients [198]. Compared with all 3 norm groups, modal score categories for sleeping problems were high. The study groups were similar regarding most baseline characteristics, but several P values found suggested differences between the study groups. Marginally higher socioeconomic status (SES) and more comorbid neurological and less cardiac diseases were observed in the intervention group. In the control group, relatively more patients reported back pain, were taking medication at the baseline, and had returned to work at intermediate assessment. In general, more than half of the patients had suffered from their chronic fatigue or pain condition for over 2 years before entering the rehabilitation and most had received prior (specialized) care for this (Table 3).

Table 3. Participant baseline characteristics.

Variable	Intervention (N[1]=159)	Control (N=116)	All (n=275)	Group difference t or X^2 [1]	*P* value
Age (years), mean (SD)	44.2 (11.55)	44.9 (11.42)	44.5 (11.48)	t_{273}=−0.5	.60
Female gender, N (%)	104 (66.7)	88 (73.9)	192 (69.8)	χ^2_1=1.7	.19
Socioeconomic status score[2], mean (SD)	−.05 (0.95)	−.36 (1.28)	−.18 (1.12)	t_{272}=2.223	.03
Returned to work (at intermediate), N (%)	16 (10.3)	24 (20.2)	40 (14.5)	χ^2_1=5.4	.02
Highest educational level (N=132)[3], N (%)				χ^2_3=2.1	.56
Primary school	1 (1.3)	0 (0.0)	1 (0.8)		
Lower secondary	21 (27.3)	12 (21.8)	33 (25.0)		
Higher secondary	28 (36.4)	19 (34.5)	47 (35.6)		
Tertiary education	28 (36.4)	23 (41.8)	51 (38.6)		
Work status, N (%)				X^2_3=1.6	.67
Full-time employed	24 (15.1)	18 (15.5)	42 (15.3)		
Fully absent	55 (34.6)	48 (41.4)	103 (37.5)		
Partially absent	39 (24.5)	31 (26.7)	70 (25.5)		
Unemployed	38 (24.4)	22 (18.5)	60 (21.8)		
Pain locations, N (%)					
Neck or head	77 (49.4)	61 (51.3)	138 (50.2)	X^2_1=.01	.76
(low) back	92 (59.0)	92 (77.3)	184 (66.9)	X^2_1=10.3	.001
Upper extremities	57 (36.5)	44 (37.0)	101 (36.7)	X^2_1=.01	.94

Lower extremities	59 (37.8)	57 (47.9)	116 (42.2)	X^2_1=2.8	.09
Symptom duration, N (%)				X^2_3=1.9,	.60
3-6 months	13 (8.4)	10 (8.4)	23 (8.4)		
6-12 months	35 (22.6)	20 (16.8)	55 (20.1)		
1-2 years	36 (23.2)	26 (21.8)	62 (22.6)		
More than 2 years	71 (45.8)	63 (52.9)	134 (48.9)		
Symptom course, N (%)				X^2_1=.10,	.95
Deteriorating	100 (64.1)	76 (63.9)	176 (64.0)		
Improving	23 (14.7)	19 (16.0)	42 (15.3)		
Comorbidities, N (%)					
Cardiology	19 (12.2)	25 (21.0)	44 (16.0)	X^2_1=3.9,	.048
Neurology	16 (10.3)	0 (0.0)	16 (5.8)	X^2_1=13.0,	<.001
Endocrinology	14 (9.0)	10 (8.4)	24 (8.7)	X^2_1=.03	.87
Pulmonology	24 (15.4)	19 (16.0)	43 (15.6)	X^2_1=.02	.90
Visited other care providers during programme, N (%)				X^2_4=1.7	.79
Never	54 (36.2)	44 (37.3)	98 (36.7)		
1 – 2 times	49 (32.9)	37 (31.4)	86 (32.2)		
3 times or more	46 (30.9)	37 (31.3)	83 (31.1)		
Body Mass Index (kg/m2), mean (SD)	27.0, 5.16	27.1, 5.13	27.1, 5.13	t_{270}=-.181	.86
(Very) low oxygen absorption capacity (Åstrand)[4], N (%)	44 (38.3)	36 (42.3)	80 (40.1)	X^2_1=3.0	.81
Symptom recurrence (yes), N (%)	93 (59.6)	73 (61.3)	166 (60.4)	X^2_1=.08	.77
Previous specialized medical care received (yes), N (%)	101 (64.7)	85 (71.4)	186 (67.6)	X^2_1=1.4	.24
Treated elsewhere (baseline), N (%)	81 (52.3)	64 (53.8)	145 (52.9)	X^2_1=.06	.80
Medication intake, N (%)	104 (66.7)	93 (78.2)	197 (71.6)	X^2_1=4.4	.04

[1] N: number of participants, t: Student T, X2: Chi-square (if Levene's test for equality of variances was significant, then equal variances were not assumed)

[2] Socio-economic status index by neighbourhood is derived from characteristics of the people living there: their education, income and position in the labour market. The higher the index, the higher SES. Nationally, the mean is 0, the standard deviation is 1.09, and the minimal and maximal scores are -6.75 and 3.06.

[3] Highest education data was incomplete, due to an administrative error. Missing values (n=143) were group independent.

[4] Physical condition: age and weight corrected oxygen absorption capacity measured with the sub-maximal Åstrand performance test. Missing values are due to exclusion of observations under 120 beats per minute, or testing contra-indications (i.e., high blood pressure).

5.4.3 Qualitative results

Codes describing intervention group patients' (4 males, 4 females) responses to open questions about expected outcome changed because serious gaming did not contain the domains of physical symptoms, physical functioning, or subjective fatigue. However, in interviews with patients with the highest expectations (score 8 or 9 out of 10; 2/8, 25%), possible benefits in the realms of emotional functioning (i.e., depressed mood and obsessive or compulsive behaviour) and concentration problems were voiced. These outcome domain labels were attached to patients' expressions about expectations of improved awareness, regulation, or transcendence of negative thought and lack of interest (depressive mood), problems in decision making (obsessive or compulsive behaviour), or losing focus on tasks (concentration problems), which is (partly) illustrated by the following quotes:

"What I gain from it? Yes, maybe that when you're busy with something…that you're really focused on it and not being distracted…Yes, it's clear that I have that focus more."

"In your daily life you are confronted with things that you, or I in any case, did not initially see as stress…Well, I often travel by train, and sometimes things annoy me, but I usually ignore it. Now I have something like: I can talk to them…So, you are irritated, and at the moment you notice it you are annoyed, so it's getting worse…Yes, you can just make it go away so that it does not adversely affect your mood."

Following these perceptions in a minority of patients, it was proposed that serious gaming generally facilitates a small amount of additional change regarding the primary outcomes of fatigue and emotional functioning (see trial registry). Moreover, additional change for patients in the intervention group was expected to be reflected by observing stronger decreases in scores based on depression and insufficiency subscales of SCL-90 and concentration problems subscale of CIS.

5.4.4 Quantitative outcome assessment

At the baseline, participants reported on average moderate pain intensity, high fatigue, and high psychological distress levels compared with norm group

averages (Table 4). After treatment, average outcome score levels were subsequently mild, higher than average, and "average" (relative to healthy norm groups).

Table 4. Primary outcome scores.

Outcome	Intervention group		Control group	
Measure and time	N	Mean (*SD*)	N	Mean (*SD*)
Current pain intensity Numerical rating scale (0-100) [53]				
t0	156	56.60 (*32.27*)	119	58.71 (*30.92*)
t1	156	35.79 (*25.80*)	119	35.03 (*26.31*)
t2	150	26.08 (*24.07*)	118	29.81 (*25.56*)
Fatigue Checklist Individual Strength (CIS) [51] [1]				
t0	154	110.97 (*18.63*)	118	108.05 (*15.88*)
t1	154	84.05 (*26.51*)	118	83.42 (*24.57*)
t2	147	60.68 (*27.04*)	116	65.62 (*26.07*)
Catastrophizing; Pain Coping & Cognitions List (PCCL) [54][2]				
t0	126	3.54 (*0.94*)	97	3.46 (*0.86*)
t1	126	2.68 (*0.86*)	97	2.60 (*0.93*)
t2	121	2.10 (*0.90*)	95	2.05 (*0.88*)
Psychological distress; Symptom Check List (SCL-90) [52][3]				
t0	156	195.25 (*50.55*)	119	193.21 (*49.40*)
t1	156	161.93 (*43.21*)	119	151.18 (*35.92*)
t2	149	120.45 (*32.96*)	117	118.26 (*28.90*)

N: number of observations, t0: measurement at baseline; t1: intermediate (after 8 weeks of treatment); t2: posttreatment (after 16 weeks of treatment)

[1] Norm information for the checklist individual strength: average for healthy controls: mean=41.5, *SD*=19.8; average of a norm group of patients with chronic fatigue syndrome: mean=113.3, *SD*=14.6.

[2] Some data is missing by the design of routine outcome monitoring; PCCL scores are absent for very low pain intensity scores.

[3] Baseline mean is high as compared to a norm group of patients with Chronic Pain.

The final multivariate mixed linear model included a study group dummy instead of the site index, SES scores, and intermediate return to work as (potential) confounding variables (Textbox 2). Model fit did not improve by adding pain location or comorbidity factors, medication intake, and amounts of particular kinds of psychotherapy received.

Textbox 2. Specified multivariate linear mixed model of standardized primary outcome scores.

A predicted (standardized) value for an individual patient on any of the 4 primary outcomes at a certain point in time is calculated as the sum of a random intercept regarding the outcome type (1=pain intensity, 2=fatigue, 3=catastrophizing, 4=psychological distress) and fixed-effect parameter estimates for the following:

- intervention group membership (1=intervention, 2=control [reference category]);
- time 0-1 (baseline=1 relative to intermediate=3 [reference category]);
- time 1-2 (post=2, relative to intermediate=3);
- socioeconomic status (SES) multiplied by the SES score;
- being returned to work at intermediate assessment;
- interaction between intervention and time 0-1; and
- interaction between intervention and time 1-2.

In addition, patterns of change in all 4 primary outcomes taken together throughout the rehabilitation programme of each study group were visualized (Figure 2), showing that outcome scores improved in parallel before exposure to serious gaming and improved relatively more for the intervention group between intermediate and posttreatment.

The multivariate mixed model, which assumed equivalent changes across the 4 primary outcomes, indicated statistically significant improvement over the first half (beta=−.805, SE=0.042, *P*<.001) and the second half (beta=−.473, SE=0.034, *P*<.001) of treatment. The parameter estimate for the interaction effect (simultaneously on the 4 outcomes) of group × time 1-2 (representing the interval between intermediate and posttreatment) favoured the intervention group to a very small extent by −.119 (SE=0.046, P=.009); this equals to 8.59% of the total amount of outcome change within the intervention group.

From the intermediate to posttreatment assessment, 48.7% (73/150) and 2.7% (4/150) of the patients in the intervention group reported reliable improvement and decline, respectively, in one or more primary outcomes (Figure 3). In the control group, these proportions were 40.7% (48/118) and 7.6% (9/118). Furthermore, proportional distributions of reliable improvement, stability, and deterioration were not different between the groups (χ 2 1=5.677, P=.06).

Figure 2. Patterns of change during rehabilitation in average standardized scores over the 4 primary outcomes in comparison between groups

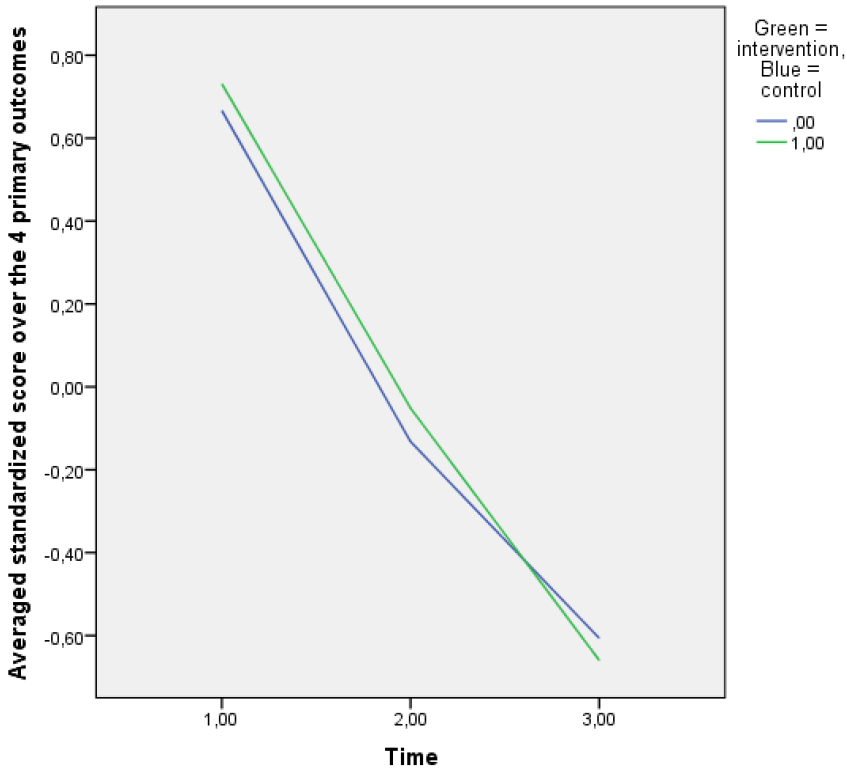
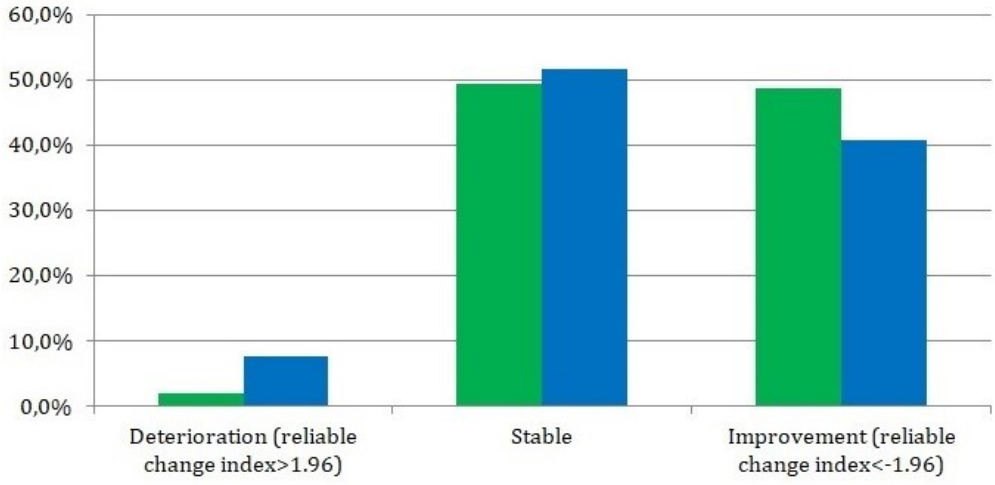


Figure 3. Within group proportions for reliable improvement or decline in all 4 primary outcomes between intermediate and post treatment



Second, univariate tests for a hypothesized group effect on changes in unstandardized CIS concentration problems and SCL depression and insufficiency scores (Table 5) resulted in a two-sided P value below the adjusted Holm-Sidak criterion level (alpha<.017) only for a comparatively stronger decrease in intermediate to post SCL depressive symptom scores for the intervention group (b=-2.74, *P*=.011).

Observations on secondary outcomes showed generally high scores for PGIC, general health, functioning (distance perceived relative to before the onset of pain or fatigue complaints and current satisfaction), and treatment satisfaction ratings (Table 6). Moreover, no group differences in secondary outcome variables were observed at posttreatment or in change since the intermediate assessment. A summary of developments in primary and secondary outcomes throughout the second part of the rehabilitation programme is presented in S2 Appendix, Figure 2.4.

Finally, log data within the intervention group showed that 1 patient logged in but did not play the game, 12 played up to 50% of the game, 24 played 50%-75% of the game, 110 played 75%-100% of the game, and 9 patients continued to play a second time. Of all, 54.7% (87/156) of the patients completed 16 “encounters,” which equals to completing the game precisely once. Notably, completed encounters averaged 14.5 and ranged from 0 to 28. Among patients who did not finish the game (60/156, 38.5%), relatively few had reported completing tertiary education (5/21, 23.5%; χ 2 3=10.075, P=.02) or previously receiving specialist care (33/60, 55.0%; χ 2 1=4.23, P=.04). A debriefing session was attended by 151 patients. Groups with low adherence were too small to provide valid efficacy estimates within each.

Table 5. Univariate linear mixed modelling results.

Subscale time[1]	**Intervention group** N[1]	Mean (*SD*)	**Control group** N	mean (*SD*)	Effect	Unstandardized regression coefficient *b* (SE)	*P*-value[2]
Symptoms Checklist depression subscale							
T0	156	40.49 (12.22)	119	39.87, (12.69)	t0-1[3]	-8.50 (.92)	<.001
					t1-2	-7.20 (.71)	<.001
T1	156	31.99 (11.31)	119	28.89, (8.94)	t0-1*X[4]	2.52 (1.40)	.07
T2	149	24.85 (8.64)	117	24.50, (7.95)	t1-2*X	-2.75 (1.07)	.01
Symptoms Checklist insufficiency subscale							
T0	156	24.63 (6.68)	119	23.96, (7.15)	t0-1[3]	-4.5 (.48)	<.001
					t1-2	-4.0 (.43)	<.001
T1	156	20.1 (6.05)	119	18.62, (5.55)	t0-1*X[4]	.82 (.76)	.27
T2	149	16.11 (5.57)	117	15.97, (5.41)	t1-2*X	-1.36 (.65)	.04
Checklist Individual Strength concentration problems subscale							
T0	154	26.69 (7.62)	118	24.71, (7.34)	t0-1[2]	-4.84 (.70)	<.001
					t1-2	-5.96 (.55)	<.001
T1	154	21.85 (7.80)	118	21.03, (7.20)	t0-1*X[4]	-1.25 (1.06)	.24
T2	147	15.84 (7.88)	116	16.27, (7.24)	t1-2*X	-1.17 (.83)	.16

[1] N: number of observations, t0: measured at baseline; t1: intermediate (after 8 weeks of treatment); t2: posttreatment (after 16 weeks of treatment)

[2] Sidak-Holm corrected alpha criterion levels were applied to the three primary outcomes, being .017 for the lowest P-value, .025 for the second smallest *P*-value, and .05 for the largest *P*-value.

[3] t1 parameters in this table are multiplied by -1, because time 1 (index=3) was the reference category.

[4] X: intervention group

Table 6: Secondary outcomes by group and time

Outcome	Intervention group t1[1] (N[1]=156)	t2 (N=150)	Control group t1 (N=119)	t2 (N=118)	Δ Group (by time) t or X^2 [1]	P-value
Patient global impression of change, N (%)					X^2_6= 3.3	.77
• Much deteriorated	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.1)		
• Slightly deteriorated	5 (3.2)	4 (2.8)	2 (1.7)	5 (4.3)		
• Stable	16 (10.3)	10 (6.9)	25 (21.0)	6 (5.2)		
• Slightly improved	97 (62.2)	46 (31.7)	63 (52.9)	41 (35.3)		
• Much improved	37 (13.5)	85 (58.6)	28 (23.5)	63 (54.3)		
Subjective health and functioning, mean (SD)					T_{266}=-1.16	.25[3]
• General health	55.45 (24.18)	71.23 (22.57)	57.97 (23.17)	71.90 (20.39)		
• Functioning 'level' and 'distance'	46.05 (25.81) 40.12 (25.34)	70.19 (25.22) 55.47 (32.10)	50.02 (25.66) 42.04 (27.65)	69.78 (24.53) 52.85 (31.37)		
Treatment satisfaction, mean (SD)						
Rating programme	NA[4]	8.33, 1.20	NA	8.06, 1.46	T_{266}=1.65	.10
Recommend programme to other patients, N (%)					X^2_3=4.8	.09
• Certainly not	NA	0 (0.0)	NA	0 (0.0)		
• Probably not		4 (2.7)		9 (7.6)		
• Probably yes		40 (26.7)		37 (31.4)		
• Certainly yes		106 (70.7)		72 (61.0)		
Expectations met, N (%)					X^2_3=4.7	.20
• Not at all	NA	0 (0.0)	NA	3 (2.5)		
• Mostly not		14 (9.3)		12 (10.2)		
• Mostly		84 (56.0)		58 (49.2)		
• Completely		52 (34.7)		45 (16.8)		

[1] N: number of participants, t1:at intermediate assessment, t2: at post assessment, t: Student t, X^2: Chi-square

[2] If data are available at intermediate and post assessment group differences were assessed in change from intermediate to post assessment.

[3] Group differences were tested in change of the average scores over the three items (that together formed an internally consistent scale). Similar results were obtained if procedure MIXED or repeated measures ANOVA was used.

[4] NA: Not Applicable

5.5 DISCUSSION

5.5.1 Summary of evidence

In this study, we aimed to determine to what extent and in what respect a novel 4-hour mindfulness-based serious gaming intervention is effective in facilitating additional change in relevant physical and emotional functioning outcomes during a regular multidisciplinary rehabilitation for patients with CP or FSS. Furthermore, we studied whether such effects have clinical relevance for health improvement as conceived by patients themselves and whether these effects depend on the varying adherence within a regular care setting. Patients with mainly (low) back pain with comorbid psychosocial problems were found to adhere well to additional serious gaming during regular multidisciplinary rehabilitation, resulting in a very small (merely statistical) strengthening effect on the reduction of physical and emotional symptoms, as a whole, and of depressive symptoms, in particular. The effect of serious gaming alone, as a relatively small additional programme component, did not reach clinically relevant levels; this was also suggested because patient impressions of health change and treatment satisfaction showed no improvement compared with the regular programme, which already showed high satisfaction and treatment success rates. Nonetheless, within this context of multidisciplinary rehabilitation, 4 additional hours planned for serious gaming (4% of therapy time) in small groups, largely without direct professional support, accounted for 8.9% of the total average primary outcome change for the intervention group during rehabilitation.

Several insights arise from relating these results to those of previous studies on similar interventions. First, the very small effect size found in this study suggests a relatively weak effect compared with the small effect sizes found in previous studies. Those studies included evaluations of the effect of exposure to games on health outcomes with pragmatic trial designs [288, 289], as well as systematic reviews and meta-analyses of randomized controlled studies on the efficacy of games for various clinical and behavioural outcomes [30, 43]. Plausible explanations for a lower estimate in this study are the relatively low intensity and late supply of serious gaming relative to other efficacious psychotherapy (including mindfulness) interventions offered through other modalities of multidisciplinary rehabilitation. For any such short-term component in multidisciplinary rehabilitation, an effect large enough to be generally noticeable

to patients would be extraordinary within the target population, and many patients may already have benefited from "traditional" means to improve.

Second, both present and earlier findings suggest that changes with mindfulness approaches occur simultaneously across outcomes [290]. Still, our quantitative and qualitative results combined also add specifically to the anecdotal evidence from previous randomized trials that depressive symptoms are a plausible target for serious gaming [289, 291].

Third, our findings indicate a possible relative efficiency of the independent usage and guidance in groups that constitute a "blended" form of serious gaming. To illustrate, the effect size estimate found in this study approaches the estimates found in a previous meta-analysis on the outcomes of computer (internet)-supported therapy across chronic somatic conditions (standardized mean difference ranging between 0.17 and 0.21 across outcomes) [77]. Therefore, the results of this study indicate, but do not prove, that serious gaming could serve as a complement or substitute to (parts of) other sorts of computer-based or blended treatments aimed at allocating scarce professional guidance more efficiently.

Finally, there was doubt, before this study, on whether the adherence and efficacy of computer-based interventions are readily transferable to contexts, as in this study, wherein patients are recruited from a clinical setting instead of being openly recruited from general populations via the internet or other media [119]. This study sheds light onto this transferability issue by showing that a relatively high level of adherence can be achieved within a regular health care context where self-selection for the modality is limited, when a serious gaming supplement is offered "by default," based on understandings of usage factors [218].

5.5.2 Strengths and limitations

Strengths of this study relate to the novelty of the serious gaming approach, statistical power, and the apparently favourable conditions for pragmatic research. This evaluation addresses a unique combination of setting, patient, and intervention characteristics (mindfulness approach and blended mode of supply). Achieving the predetermined required sample size for observing a modest effect with reasonable chance responds to previous reviews on the effectiveness of games for health that found promising results for mainly small, underpowered

studies [43, 282]. Furthermore, this study has taken account of Type I error risk through outcome multiplicity, factors of non-usage, and risk of biased patient expectations through the informed consent procedure. In the execution of the study, we encountered occasional unintended difficulties in accessing the game (i.e., forgetting passwords) but did not encountered problems or threats to internal validity, besides those inevitable and known in the protocol phase. The precision of key results was supported by the results of sensitivity analyses after outlier removals, alternate outcome standardization, removal of incomplete cases due to treatment dropout, and extensions and simplifications (e.g., exclusion of baseline data, inclusion or exclusion of potential confounding variables) of the prediction model. Mixing quantitative and qualitative outcome data led to unambiguous findings regarding the size, outcome domains, and the clinical relevance of serious game effects. Regarding the external validity, this application of pragmatic methods adds complementary insight into the effectiveness of serious gaming for patients in regular health care settings beyond controlled clinical trial conditions. The inclusive patient recruitment strategy reflects the reality of a regular care setting to which the results are to be generalized.

However, several study weaknesses should be considered, comparing this study with supposedly ideal circumstances for a randomized controlled (multicentre) trial. Not applied for practical reasons were broader recruitment of treatment settings, researcher control on selection procedures, the use of an individual or site-level randomization procedure for balancing unobserved characteristics between study groups, inclusion of certain measures (long-term follow-up, objective outcomes, functional interference, quality of life, and participation), and collections of cost data. In addition, intervention group participants were aware that they received a novel treatment component. However, this is not expected to have influenced the results as an insignificant association was observed between outcome expectations of serious gaming and health outcome change levels (intermediate to posttreatment) within the intervention group. Adding an additional component to an already intensive treatment programme has neither been deemed likely nor intended to increase cost-effectiveness at present, but may offer useful insight for achieving this in the future. Although previous studies have suggested that effects of serious games for behavioural change are retained [30], it remains uncertain how a very small reinforcing influence on patterns of outcome change that started earlier during treatment will develop further in time.

Furthermore, a lack of more stringent diagnostic methods at inclusion poses an internal validity threat. Data are also missing about characteristics of patients who dropped out during the first part of the programme. Moreover, present results suggest that (everything else being equal) additional serious gaming adds very little to the outcome improvement, but intervention group participants did not reach more favourable outcome levels at posttreatment. A possible explanation is that control group symptom levels were slightly lower overall because of an effect of recruitment that was too small to observe. Besides, not all expected outcome domains found through the qualitative research were confirmed with quantitative results; this might also be attributed to a lack of power as pre calculations have not been based on an increasing number of statistical tests. Finally, generalizability is limited by the convenient selection of 4 locations from a single Dutch care centre.

5.5.3 Suggestions for research and practice

In light of previous research, the very small positive effect on relevant outcomes found in this powerful pragmatic study reaffirms that both caution and optimism about the effectiveness of serious games as a treatment facilitator are warranted. Findings imply that serious gaming holds potential, as for the present mindfulness-based approach to it, but requires further investigation before wider dissemination within multidisciplinary rehabilitation programmes or other regular health care settings (e.g., psychological therapy). From patients' point, expectations on potential benefits are to be placed in perspective, that is, results merely suggest that multidisciplinary rehabilitation based on a biopsychosocial approach (i.e., one that includes mindfulness approaches to learning to live with CP or FSS) with generally modest effects (i.e., offer little assurance for recovery) could be somewhat improved (in a slight, merely statistical, degree) by adding serious gaming as a modality. We do not suggest that additional serious gaming causes more patients to experience clinically relevant treatment effects. Nonetheless, the study results do suggest that the delivery of a small part of an evidence-based treatment by means of a serious game can be trusted. Therefore, researchers should continue to pursue adequately powered and, if possible, RCTs when aiming to assess the effects of (mindfulness-based) serious gaming.

As part of a general search for effective combinations of approaches, techniques, and modalities to intensive rehabilitation programmes, the serious gaming

approach requires further theoretical refinement as to know how and when clinically relevant benefits are achieved by which patients and why. The current state of evidence provides little support as to identify those circumstances in which patients with CP or FSS will likely have best experiences and outcomes from which (computer-based) biopsychosocial or alternative treatments and why [14, 233, 292]. In this regard, our findings specifically point toward very small positive effects when (mindfulness-based) serious gaming is presented later on in a rehabilitation process to patients with chronic back pain and comorbid psychosocial problems. Patients, policy makers, and professionals must be aware of the ongoing developmental stage, wherein the accumulation of knowledge is needed before the full potential of serious gaming can be realized routinely and efficiently into complex health care systems [30, 293]. Thus, to achieve the highest potential of serious gaming for health, more theoretically oriented and context-sensitive studies are needed in addition to more powerful outcome assessment trials. To facilitate progress, researchers need to focus on a broad range of research questions about when and which kinds of serious games are (cost-) effective, for whom, compared with other treatment options, and why. This endeavour requires (1) hypotheses-driven process evaluations alongside trials (using quantitative, qualitative, or mixed methods); (2) transparent and universal reporting on the qualities of the methodology (i.e., eHealth CONSORT statement additions [91]), serious games for health (rationale, functionality, and data security [70]) and behavioural change content (theoretical approaches, change strategies, and presentation methods [17]) in trials, (3) implementation research investigating organizational, professional, patient, and intervention factors; (4) impact assessment as dependent on actual reach; and (5) health technology assessments.

5.5.4 Conclusion

Based on a powerful natural quasi-experiment, the results of this study suggest that serious gaming, as an additional modality for mindfulness intervention of short duration during regular multidisciplinary rehabilitation, adds very little to reducing physical and psychological symptoms in patients with CP or FSS (i.e., indicated with chronic back pain and concomitant psychosocial problems). In addition, the results hint, but cannot yet prove, that these very small benefits are nonetheless relevant in terms of efficiency if one considers how little (extra) time

it costs from scarce expert care providers. An effect with respect to depressive mood may exist that a minority of patients conceive as relevant for their daily life. Moreover, the findings clearly support a generally good adherence to a blended form of serious gaming in a regular care setting. Taken into account the conditions of serious gaming in this study (i.e., relatively low intensity compared with the complete treatment programme that patients received), the results fit the expectations created by previous studies that generally found slightly higher (small) effects on behavioural and clinical outcomes (i.e., studies on serious games in various populations or studies on computer-based interventions in patients with CP or FSS). Therefore, the potential of serious games for being effective in changing behavioural and clinical outcomes across targeted populations is reaffirmed and further (theory-driven) research on serious gaming aimed at predictably (cost-)effective applications for individual patients across health care settings encouraged.

Abbreviations:

- **CIS:** Checklist Individual Strength
- **CP:** Chronic pain
- **FSS:** Functional somatic syndromes
- **NPC:** Nonplaying character
- **PGIC:** Patient's global impression of change
- **RCI:** Reliable change index
- **RCT:** Randomized controlled trial
- **SCL-90:** Symptoms Checklist
- **SES:** Socioeconomic status

6 PROCESS EVALUATION

This chapter was offered for publication in Journal of Medical Internet Research on May 22, 2019.

Title: Serious gaming during multidisciplinary rehabilitation for patients with chronic pain or fatigue symptoms: Realistic process evaluation

6.1 ABSTRACT

Background: Serious gaming could support patients in learning to cope with chronic pain or functional somatic syndromes and reduce symptom burdens. To realize this potential, insight is needed into how this could work, why, for whom, and in what actual treatment circumstances.

Methods: Inspired by a realist approach, process evaluation methods were embedded before, during, and after a two-armed natural quasi-experiment (n=275). Changes in health outcome over time were compared between two groups of patients with interfering chronic pain or fatigue symptoms: 1) those who received a short additional blended mindfulness-based serious gaming intervention during a regular multidisciplinary rehabilitation programme and 2) those who did not. Prior to inspecting outcome data, stakeholder focus group and patient semi-structured interview data were coded for configurations of intervention characteristics (I) in context (C) that activate mechanisms (M) for producing outcomes (O). Subsequently, hypotheses were formulated that could be tested on quantitative data using multiple regression and (moderated) mediation models.

Results: Qualitative methods showed that self-discrepancies perceived by patients during serious gaming were a necessary trigger (M) for learning results with respect to self-awareness in moments of daily social interaction (O). Characteristics of serious gaming intervention (I) in context (C) that recipients considered important for gaming acceptance or learning results included design qualities, the relative advantage of an experiential learning opportunity, compatibility within rehabilitation treatment with a consistent approach and distinctive modality, (limited) flexibility to adjust to the personal preferences and contexts of the users, patients' age and styles of managing stress or pain, provider role perceptions, and local intervention planning and facilitating processes. Quantitative methods showed that very small study group differences in self-reported depression, pain and fatigue changes ($-.07<\beta<-.17$, all 95% confidence interval upper bounds <0) were mediated by group differences in mindfulness ($\beta=.26$, 95% CI=.02-.51). Mindfulness changes were also positively associated with patient involvement in serious gaming (n=114, $\beta=.36$, P=001). Acceptance of

serious gaming was lower in older patients. Outcome changes were stronger in patients that reported lower active coping with stress and pain coping before serious gaming. Finally, learning results and acceptance varied by indicators of local planning and facilitation of serious gaming.

Conclusions: This study developed a tentative programme theory about how and why serious gaming can additionally support learning about coping for reducing burdens of chronic pain or fatigue symptoms in certain patients and actual intervention delivery conditions. Future research can elucidate which findings are fallible, extendable, and transferable across future serious gaming contexts. This supports decisions for designing, allocating and tailoring serious gaming for optimal patient chances of important health benefit.

Trial registration: This study was registered in the Netherlands Trial Registry NTR6020 on June 10th, 2016.

6.2 INTRODUCTION

6.2.1 Background

Serious gaming could someday have substantial impact in reducing burdens of chronic pain (CP) or functional somatic syndromes (FSS). CP and FSS are both prevalent and debilitating conditions with high social and economic burdens [8, 9]. CP is defined by pain that persists longer than a usual 3- to 6-months of organic recovery that may but does not need to have, an organic cause [9]. Functional somatic syndromes (FSS) are characterized by persistent patterns of bodily symptoms, including pain, fatigue, tinnitus, bowel complaints that cannot be sufficiently explained by a specified pathology after adequate examination [8]. Chronic low back pain, which is both a common CP and FSS condition, could be associated with higher total worldwide burdens of functional disturbance than any other disease [294]. In Western countries, economic costs of sick leave and early retirement exceed the total amount of medical expenditures associated with CP [295, 296].

A serious game is a kind of computer-based intervention that not only aims to inform, instruct and modify, but also to give 'fun' [30]. A growing body of evidence suggests that serious games can have positive effects on patient knowledge, behaviour or clinical outcomes [30, 43, 289]. Maybe, a serious game can reduce depressive symptoms by as much as a usual face-to-face delivered cognitive behavioural therapy [282, 289]. A particular serious game (LAKA) was developed, based on a mindfulness model, to educate patients with chronic somatic symptoms about coping for reducing their burdens [297]. Previous results of a natural quasi-experimental outcome evaluation, in which most of the participants had chronic back pain and concomitant psychosocial problems (n=275), suggested that four hours of blended serious gaming intervention (with LAKA) during multidisciplinary rehabilitation led to very small (average) additional reductions in somatic and emotional symptoms.

This report presents a realistic approach to embedded process evaluation that aims at building transferable explanations of what works in certain patients and settings. Specifically, explanatory insight is developed into how the modality of serious gaming could contribute in facilitating clinically important yields for certain patients in a context of regular (multidisciplinary) treatment.

6.2.2 Management of chronic pain and functional somatic syndromes

For managing the burdens of CP and FSS, biopsychosocial approaches are considered effective [9]. Accordingly, treatment regimens may include steps of conservative medication, psychotherapy, and physiotherapy, and, if not sufficient: a multi- or interdisciplinary rehabilitation programme [298]. Multidisciplinary rehabilitation programmes can vary in content but commonly include medical, psychological, physical, and occupational interventions [14, 299]. Meta-analyses on biopsychosocial and complementary approaches generally suggest positive, small or medium sized and heterogeneous effects of biopsychosocial interventions on symptoms and functional interference [14, 233, 300-303]. Individual patient chances of clinically relevant intervention benefits depends on better understandings of (1) symptom mechanisms at biological levels [304], but also of (2) how various psychosocial interventions (approaches, strategies, and modalities) facilitate improvement of physical and emotional functioning across patients and settings at acceptable cost [27, 305]. With regard to the latter, current interest goes to opportunities of computer supported intervention [26, 159].

6.2.3 How and why biopsychosocial treatment approaches work for whom and when

Biopsychosocial interventions commonly target improvement through the 'top-down' moderation of central sensitization processes as a mechanism of somatic symptoms [10]. Accordingly, studies found that psychosocial changes with respect to coping with stress and pain, avoidance beliefs, rumination, acceptance, or catastrophizing, mediate treatment effects on somatic symptoms or functional interference. [306-308]. Such psychosocial changes may be targeted effectively by promoting individual properties of mindfulness (i.e. neurological processes of self-awareness, self-regulation, and self-transcendence) in response to symptoms, or by restructuring cognitive antecedents of supposedly dysfunctional emotions and behaviours [19, 20, 80, 290, 306, 309, 310]. The difference between these approaches, with regard to affected mechanisms and of outcome change levels and respects, is of recent interest [20, 311]

Furthermore, literature about patient factors for effectiveness provide limited evidence to inform practice. Some studies claimed that demographic and psychological differences between patients may not predict clinically important

variation in treatment effects [160, 312]. This would suggest that similar treatment effects can be expected for everyone, regardless of age, gender, or appraisals. Other studies, however, stressed that baseline fear-avoidance beliefs, pain acceptance, or depressive symptoms can predict treatment gains to some extent and should therefore be targeted early or additionally in treatment [27, 82, 305, 313-315].

Furthermore, specifications are largely lacking for characteristics of interventions and treatment environments that could be responsible for varying degrees of effectiveness. A body of experimental evidence supports that computer-based intervention (e.g., delivery over the internet) provides modest chances for reducing symptom burdens, similarly to face-to-face group therapy, but it is unclear how this finding transfers from self-selecting participants to wider populations and settings [305]. Nonetheless, studies have found varying levels of effectiveness between patients and study settings that require explanatory research that; (1) consider a multitude of potential factors of heterogeneous treatment effects (i.e., fidelity of implementation, patient physical status, programme compositions, comparisons, and outcome measures); (2) deal with interdependence and interactions between factors, and (3) develop theory [27, 313, 315-317].

6.2.4 How and why serious gaming may work, for whom, and when

Previous studies provide plausible rationales on how serious games could enhance the effectiveness of existing treatments but lacks high-quality empirical support. Gaming or virtual reality applications could offer relative advantageous experiential and motivational qualities in processes of extinction of phobias, distraction from pain, repetitive physical or cognitive training, or learning about cognitive antecedents (e.g., self-efficacy) of health behaviour [180, 237, 242]. Moreover, serious gaming may strengthen the engagement of the patient and efficacy of the treatment by enhancing intrinsic motivation, positive affect, and sense of presence when processing efficacious behavioural change content [242, 281].

Studies that explored outcome change attributions by intervention features (e.g., participatory design, duration), user (patient or learner) characteristics (e.g., gender, age, intelligence, gaming experience) provided some preliminary indications regarding for whom and when games are particularly

effective [30, 318, 319]. However, previous studies have also emphasized the unpredictable and context-sensitive nature of individual experiences of serious gaming [245, 250]. Debriefings may deal with this in guiding important recipient experiences after serious gaming towards targeted individual learning results [251].

6.2.5 Study objectives

This study aims to support decision-making on ongoing development and future implementation of serious gaming such that new opportunities for clinically important health improvement may arise in certain future patients and contexts. This could be in multidisciplinary rehabilitation or other similar settings. Hereto, there is a need to support, refute, refine, and extend initial ideas about how forms of serious gaming (e.g. blended and mindfulness-based) could facilitate additional improvement in relevant health outcomes, depending on variations in the characteristics of the patients with CP or FSS and on the conditions of intervening in real health care settings. The research questions are 1) how, 2) why, 3) for whom (which patients) and 4) under what conditions of intervention delivery ('when') additional patient health outcome changes occur due to additional serious gaming in a context of treatment.

6.3 METHODS

6.3.1 Process evaluation approach

This study is inspired by and reported in accordance with a Realist Evaluation (RE) approach [46]. In process evaluation of complex 'programmes' or 'interventions' (terms are interchangeable), realist principles support a focus on theory development and contextual sensitivity [24, 320]. Hereto, a RE focuses on a 'programme theory' specified as one or more contexts (C) wherein introducing an intervention (I) triggers mechanisms (M) leads to particular changes in outcomes (O) (i.e., I-C-M-O configurations, or ICMOC's). Formulating ICMOCs can be a form of constructing theory at a 'middle-range' level of abstraction; dealing with different spheres of behaviours and structures to transcend sheer description [255]. Middle-range theories can be developed through discovery of regularities by thought, or by inferring explanations on the basis of more abstract formal theories [321]. In support of such analytic processes, several existing theories were taken from the literature throughout the project: during the design process,

when continuously interpreting developer assumptions, and when discussing feasibility study results.

6.3.2 Initial programme theory

S2 Appendix, Table 2.8, comprehensively describes initial ideas for inferring outcomes, mechanisms, and context of serious gaming that were referenced or described in earlier development stages [218, 273]. Textbox 1 shortly summarizes them as an ICMOC.

Textbox 1: intervention – context – mechanism - outcome configuration summarizing initial expectations about how serious gaming produces intended outcomes in context

A blended form of mindfulness-based serious gaming (i.e. with face-to-face debriefing) as a standard component during multidisciplinary rehabilitation (intervention) is;

- acceptable (feasibility mechanism / intervention);
- for adherence (feasibility outcome / intervention);
- by any eligible patient with a complex CP or FSS condition and in any circumstance (context).
- Thereby, it can provide complementary features, such as founds, visuals, storytelling, and covert learning strategies that trigger distinctive experiential, affective or motivational qualities (valence of affect or sense of presence) (gaming mechanism);
- to strengthen learning results with respect to 'mindfulness', coping flexibility, or psychological well-being (rehabilitation mechanism or intermediate outcome), and;
- subsequent reductions in physical and emotional symptoms (rehabilitation outcome).

Underlying explanations for ICMOs could be constructed in terms of the S-ART model of mindfulness mechanisms [42], self-determination theory [322], an eudaemonist approach to psychological well-being [39], or relational frame theory [323].

A broad conceptualization of mindfulness was considered, amongst alternatives for explaining the effects of similar intervention approaches, to be most consistent with initial developer expectations [42]. In addition, various motivational/affective processes during serious gaming were considered to potentially strengthen learning or behavioural change effects [242]. A broad range of contextual influences were anticipated [257, 258]. There were no other specific expectations than that serious gaming would be more acceptable and better adhered to under the improved delivery conditions that were informed by a previous pilot study [218].

Table 1: Steps of recruitment, data collection (A-G), and analyses (1-5).

(Protocol) step	Research activity
A	Recruit stakeholders and focus group interviews (2 sessions)
B	Recruit patients
C	Collect post-serious gaming feedback from (professional and patient) users
D	Purposively select of patients for semi-structured interviews
E	Perform semi-structured interviews with patients
F	Perform stakeholder focus group interview session 3
Step 1	Code ICMO elements across all the qualitative information, and describe I-C-M-O relationships per individual patient interview. Compare patient level findings with focus group data collected from other stakeholders.
Step 2	Interpret mechanisms on the basis of formal theory (adjudication), and formulate quantitatively testable hypotheses (before outcome inspection)
G	Retrieve of quantitative data from patient records
Step 3	Describe quantitative data triangulating qualitative data
Step 4	Test quantitative hypotheses
Step 5	Mix the results of different methods: summarize how they support, refute, refine, or extend initial expectations. Construct ICMOCs ('middle-range' theory) reflecting the findings of the present study, and propose a transferable programme theory based on formal theoretical perspectives and findings from (the contexts of) previous studies.

6.3.3 Mixed-methods design

An integrated team of researchers, trained in various quantitative and qualitative methods, carried out process analyses as part of an embedded (two-armed natural quasi-) experimental mixed-methods study protocol [273]. Quantitative methods for investigating patterns in routine clinical patient outcome assessments were overall prioritized. Four sites of a single Dutch rehabilitation centre participated where all patients received a regular standardized 16-week multidisciplinary rehabilitation programme (basic treatment). At two sites, a serious gaming intervention was provided in addition during the second half (week 9-12) of the rehabilitation programme. In two other (control) sites, the intervention was not offered. Measurements were routinely taken at baseline (t0), intermediate after 8 weeks of treatment (t1), and post-treatment after 16 weeks (t2). In short, non-intrusive qualitative data were collected before, during, and after the experiment, and analysed prior to outcome inspection for deriving testable hypotheses about indicative patterns in quantitative data (see addendum to registration in the Dutch trial register NTR6020). Further details of embedding

steps of qualitative and quantitative process evaluation methods are presented in table 1.

6.3.4 Setting and participants

Settings and participants were as reported in the outcome evaluation report [297], and shortly described here. Treatment sites were similar regarding protocols, size, history, and lack of disruptive activities. Aiming for strong representation of the natural patient population (i.e. treated in independent clinics), informed patient consent was taken by care providers from each patient that received a physician indication of eligibility for regular multidisciplinary rehabilitation and entered the second part of rehabilitation treatment in the 4 participating sites. The patients consented to the retrieval of codified routinely collected clinical patient data and additional data collections for the study. A total of 275 (156 intervention group and 119 control group) participated out of 329 eligible patients (83.6%) as pre-calculated. Patients in the sample were, on average, 44 years of age (SD=11.3, range= 18-67). The female proportion was 69.8% (192/275). Almost half of the patients (134/275, 48.9%) reported symptom durations of over 2 years. Outcome evaluation results suggested that site level influences and a few differences (P<.05) between the patients of the two study groups had no (confounding) impact on outcome predictions: adding associated variables did not significantly change the fit or important parameters of the outcome prediction model.

Other participants included care providers (three psychologists, one physiotherapist), managers who were responsible for the delivery of serious gaming intervention, and stakeholders with relevant expertise (in information and communication technology, serious gaming, rehabilitation medicine, professional education, spiritual counselling). All were familiar with the setting. All received informed consent with an invitation to participate in focus group sessions.

6.3.5 Interventions

Features of the basic multidisciplinary treatment and additional serious gaming intervention offered to the intervention group were previously reported in detail [273]. A short description of LAKA is given in textbox 2.

Textbox 2: Short description of the serious game LAKA

LAKA challenges patients to take the role of a virtual character (avatar). Subsequently, game-play includes prompts for monitoring and evaluating 'satisfaction' about selected 'responses' in virtual social encounters. These optional responses are descriptions of implementation intentions for certain acts, phrases, postures in social interaction scenarios that players can select for a virtual character (avatar) that represents themselves on a virtual trip around the world. Optional responses, 5 in each instance, supposedly varied in degree of correspondence with the values of 'generosity', 'moral discipline', 'patience/ forbearance', and 'enthusiastic perseverance'. Each selected response has salient (e.g. emotional expressions) and realistic (i.e. not predictable or moralistic) consequences for the Avatar. Furthermore, neutral to positive (indirect) performance feedback reinforced the monitoring task. Moreover, scenarios prompt instructions for 3-minute focused attention or open monitoring (meditation) exercises. Encouragement is given to repeat the exercises at any convenient moments in daily life.

Tablet computers, suitable rooms with Wi-Fi connections, and automated planning of four one-hour sessions (1-6 patients simultaneously) in connection to regular therapy hours were facilitated by the clinic. Three psychologists and a physiotherapist (2 per site) provided support during the first (introduction) and fourth (debriefing) session in introducing the serious game LAKA and discussing acceptance of the technology, play experiences, and their transfer into targeted learning results. Access during the second and third sessions was organized by local staff members, but patients could also download and play LAKA at home. All recipients were expected play the game at least once, which takes 2.5 hours on average, and attended a debriefing session. This is what patients may find acceptable according to feasibility study results.

6.3.6 Qualitative data

The qualitative data collection tools (interview topics and survey questions) were based on existing classifications for possible relevant aspects of I, C, M, and O. The prioritization of topics varied with participants' expectable areas of knowledge [266]. Patient recipients were most knowledgeable on outcomes and influences of intervention in context, whilst direct care providers have more knowledge about generative mechanisms of change. Increasingly, along with progress of collecting and analysing unbiased responses, preliminary findings were shared with participants to allow their direct feedback on the programme theory construction as to further ameliorate it [266].

Focus group participants prepared for the meetings by playing LAKA and reading piloting study results and adapted delivery specifications. The first focus group included stakeholders who represented various roles and expertise areas. The research questions were openly discussed at the beginning of the session to gather independent data for programme theory development. Next, care providers and implementers specified the local implementation procedures in more detail. The second and third focus group interviews were held with two care providers working at the same intervention site. At the beginning of the second focus group, initial programme theory was discussed. During the natural experiment, care providers shared feedback informally with MV. The third focus group with care providers first addressed their post-experimental views on how recipients responded in context, including how the conditions shaped their own responses. This discussion was then enriched by sharing qualitative information that patients had given.

The first source of qualitative patient information consisted of the answers they had given on two open text questions after they had finished playing LAKA. These questions were: *"Please, describe in your own words what you experienced when you played LAKA?"* and *"Please, explain how the LAKA sessions will, according to you, contribute to your daily life?"* Furthermore, semi-structured interviews were held with patients. These interviews were held with 1) intervention group patients who were purposively selected by differences in outcome expectations, and 2) control group participants matched on important baseline variables. They took place when patients had completed their rehabilitation programme until data saturation (once asking patients about 3 good and 3 bad things about serious gaming no longer helped to gather new information).

6.3.7 Quantitative data

Table 2 lists all quantitative measurement tools and times of administering. Health outcome measures were validated questionnaires of depressive mood, pain intensity and fatigue. Learning result was also measured with a Likert-scale of which previous unpublished psychometric results (good reliability, low social desirability, associations with other constructs) supported usage as a measure of mindfulness in the sampled population (See S2 Appendix, Textbox 2.4) [309, 324].

Table 2: overview of quantitative data

Programme theory element	Construct	Variable	Operationalization	Time of measure
Rehabilitation outcome	Health outcomes[1]	Depressive mood	SCL-90 depression sub-scale [198]	t0, t1, t2[2]
		Pain intensity	Numerical rating scale (current) 0-100 [196]	
		Fatigue	Checklist individual strength [197]	
Rehabilitation mechanism / Serious gaming outcome	Learning result	Self-reported mindfulness	Sum of 3 sub-scales for mental stability, forbearance and enthusiastic perseverance, e.g.,: "Also in a turbulent environment, I can concentrate well", "I remain patient until I see the solution"	t0, t1, t2
		Gaming performance	Standardized values for responses (ordinal scales 1-5)[3]	Log data
Serious gaming feasibility outcome	Implementation fidelity	Adherence	Progress: number of encounters completed Attendance of debriefing	Log data
Serious gaming mechanisms	Experiential qualities	Sense of presence	Likert-scaled scores for Involvement and realism (Igroup Sense of Presence Questionnaire)[259]	Post gaming
		Positive and negative affect	Negative and positive affect scales (PANAS) - Short form [265] (1-5)	
Serious gaming feasibility mechanism / Intervention		Game acceptance perceptions (average of technology acceptance, and game-based learning items)[4], and outcome expectations	Selected UTAUT2 items: perceived usefulness, ease of use, trust, enjoyment [188], and EgameFlow items: clear goals, challenge, and perceived learning (ordinal scale 1-7) [192] "Use the following slider 0–10 to indicate to what extent you expect that the LAKA sessions contribute to your daily life"	

Context	Patient characteristics	Demographics	Years of age Female/male Highest completed level of education Source of income (dummies: employment, absenteeism, return to work) Socio-economic status by neighbourhood	t0 or t1
		Coping	Utrecht Coping List [264], Pain Coping and Cognitions List [262]	
		Health status	Same as outcomes (see above)	
		Family problems	Yes or no	
		Work problems	Yes or no	
		Housing problems	Yes or no	
	Provider and organization	Site, professional	Identifiers of experimental site (dummy) and care provider from whom debriefing was received	Log data
Rehabilitation intervention		Treatment components	Attended hours of modules of interventions (serious gaming and other)	
Serious gaming intervention		Intervention planning	Time and dates of play (logs) and sessions (planned and attended)	
		Individual vs. group	Number of patients attending serious gaming sessions (as determined by planning)	

[1] This report omits a primary outcome measure for pain catastrophizing. In previous outcome evaluations, no indication was found that variance in this outcome was attributable to serious gaming.

[2] t0: at baseline, t1: at intermediate after 8 weeks of treatment, t2: at post after 16 weeks of treatment

[3] Data were available on the selections made by patients for their avatar (gaming performance) as they were automatically logged to support the automatic feedback system of the game. Elucidating if game scores are valid indicators of learning is a technical challenge warranting focused research attention.

[4] Selected items had the strongest factors loadings within the scales to which they belong as established in a pilot study [218]. Taken together, the items made up an internally consistent scale (Cronbach alpha=.83)

For indicating mechanisms of usage/adherence or the acceptability/playability of the serious gaming intervention, measures of individual patient perceptions about the serious gaming intervention were included in the post serious gaming feedback survey. This survey also contained measures of positive and negative affect and sense of presence (involvement and realism subscales) that could also indicate potential distinctive mechanisms of serious gaming for learning.

Finally, codified diagnostic and administrative data signalled differences in characteristics of patients, and local context or intervention circumstances disaggregated to the patient level.

6.3.8 Qualitative analyses (step 1 and 2)

All interview texts (ad verbatim transcripts) were coded by MV (in ATLAS. ti) using sensitizing concepts for I, C, M, and O unless new codes where needed to cover meanings. The first 4 patient interviews were also coded independently by MJ (2) and AZ (2). Unresolved differences were discussed with HV. Codes attached to open feedback text were counted to get a sense of the relative importance of various themes and coverage of the interview data.

Step 1 was finalized after establishing ICMO relationships per patient interview, by coding for explicit statements about relationships between positive outcome expectations, mechanism(s) and context(s) (see S2 Appendix, Table 2.9, for illustrations). Moreover, intervention or context factors were coded as barriers when argued to be related to suboptimal, weak, or absent mechanisms or outcomes. The individual patient results were compiled and compared with qualitative data obtained from other stakeholders.

In step 2, the data patterns were interpreted by establishing (1) mechanisms conceivable from (a) formal theoretical perspective(s), and (2) hypotheses that could be tested on available (uninspected) quantitative data (about variations in O by variations of I or C). Hereto, coding results and theoretical notes were regularly shared for bilateral or team discussions. Because the research protocol was ethically reviewed before data collection started, formulations of hypotheses took account of sample size limitations (avoiding too many or too complicated hypotheses) and of inability to add quantitative measurements.

6.3.9 Quantitative analyses (step 3 and 4)

R Studio (R. version 1.1.463, package: ggplot2) was used to visually explore and describe the outcome variables (between groups and over time) separately for different combinations of patient and intervention delivery characteristics (I and C). In this way, a configurational logic was also applied to quantitative data as a means to triangulate the qualitative data. Inferential statistics were calculated with SPSS v24 through applications of Pearson correlations, multivariable linear regression, and (moderated) mediation procedures (PROCESS macro version 2.16 model formats 1, 4, and 58) [325]. S2 Apendix, Table 2.10, contains a detailed overview of all quantitative analyses planned for hypothesis testing. The data (265 complete cases) provided sufficient statistical power for moderated mediation modelling unless true direct effects are very small [326]. All multivariate models were estimated using ordinary least squares regression. Study group and moderators (I or C factors) were operationalized as dummy variables. All other variables were standardized scores. Outcome change indicators were calculated as the standardized residuals after regressing t2 scores on t1 scores. Hypothesis rejection decisions were based on two-sided .05 alpha levels, and a 95% confidence interval (CI) was used for all tests of mediation or moderation that were conducted with a non-parametric bootstrap approach (generating 5000 samples by default). Models based on quasi-experimental procedures were checked for sensitivity to observed potential confounding variables that were known to possibly differ between study groups [297]. Uncorrected parameters are presented unless substantially differing from corrected ones.

6.3.10 Mixing the results of different methods (step 5)

Final middle-range ICMO's were constructed after maintaining elements of middle-range ICMOC's, including potential refinements or extensions identified in step 1 and 2, that were not refuted by the results of the quantitative analyses.

6.4 RESULTS

6.4.1 Participants

Post-serious gaming feedback data included 114 (73.1%) patients of the intervention group. Non-responders were relatively younger (mean= 40.6, SD=11.7, *P*=.02), which was the only statistically significant difference with responders (mean=45.5, SD=11.2). The four care providers (three psychologists

and one physiotherapist) who predominantly facilitated the introduction and debriefing sessions participated in focus groups two and three. Two care providers also participated in the first focus group together with a rehabilitation physician and serious gaming expert, a spiritual counsellor, an executive and ICT expert, and two managers. The eight interviewed intervention group participants varied by the conditions in which serious gaming was received (i.e., site, groups, professionals that provided support), as well as by personal factors such as age, gender, and intervention experience and outcomes (see table 4). All respondents reported having at least completed a secondary education. Interviewing of control group patients was stopped after 2 short interviews, because it did not provide useful comparative information on processes of rehabilitation without serious gaming.

Table 4: Characteristics of patient participants in interviews from the intervention group

Patient number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Age (years)	51	34	46	45	55	47	56	55
Gender (Female=1; Male=0)	1	0	0	1	0	1	0	1
Highest education level[1]	-	2	3	3	2	3	3	-
Encounters completed (min=0; max=28)	14	15	24	28	12	16	16	1
Site id	1	2	2	2	1	1	2	2
SCL depression (range: 16-80) t1[2] to t2 decrease	2	4	17	7	17	32	12	1
Mindfulness (range: 49-245) t1 to t2 increase	6	10	24	11	27	35	28	43
Perceived outcome (range: 0-10)	9	8	7	6	5	5	1	0
Negative affect (range: 0-20)	0	3	2	5	10	1	2	20
Positive affect (range: 0-20)	17	18	11	19	6	12	3	0
Involvement (range: 0-6)	6	4.5	4.5	4	3	4.75	2.25	3
Realism (range: 0-6)	6	4	2.25	3.25	3.5	2.75	3	0
Group size debriefing (min=1; max=6)	1	5	2	1	6	5	2	3

[1] Highest education 2: Secondary (high school level) as highest, 3: Tertiary (college or university level) as highest. "-": missing value

[2] t0: measured at baseline, t1: measured after 8 weeks of treatment (before serious gaming), t2: measured after treatment

6.4.2 Results of coding qualitative materials (step 1)

6.4.2.1 Learning results

Patients openly elaborated upon their experiences with serious gaming sessions. In all except 1 interview, patient perceived barriers (I or C) were found. ICMOCs emerged from 6 interviews with patients having moderate to high outcome expectations (score: 5-9/10) (see S2 Appendix, Table 2.11). This was 61 (53.5%) across all 114 survey respondents. Expressions of outcomes were considered mostly in line with sensitizing concepts for mindfulness: a heightened self-awareness with respect to tendencies for certain dysfunctional states when reacting to situations of daily life, including loss of focus of attention, rumination, rigidity, moodiness (sad, anxious, or irritable), automaticity, and prejudice. In a sub-set of patients this was also accompanied by self-regulation for being more calm, alert, self-accepting, pro-social or assertive, e.g.;

*"With the whole happening of LAKA … (patient explains) …, which makes you approach and do things less rigid and or short-sighted." (*Patient 5*)*

6.4.2.2 Serious gaming mechanisms that lead to learning results (M-O)

Intervention group patients who elucidated outcomes also spontaneously recognized supposedly active elements (i.e. resources); 'encounters', 'reflections', mental training instructions, and debriefing. These were mostly connected to a helpful form of 'reasoning' described as being 'confronted with oneself'. Explanations of this common experience involved awareness of alternate response options, emotional consequences of those responses, non-automatic processing, effort to maintain focus of attention, and transferring gaming experiences into situations of daily life, e.g.:

*"You are confronted actually… that is where awareness begins. In everyday life you often have those situations in which you do not even realize that you can go left or right. And yes, with LAKA you really get that choice and then you really have to start thinking". (*Patient 2)

Particular qualities of experience during gaming, including positive affect and 'involvement', were more often described by patients who also described positive

learning results. However, none of the participants attributed their learning results to these gaming experiences explicitly and spontaneously;

*"I was really into this, the journey across the world... and you can completely forget the world around you... Where does that help for? Maybe that when you're busy with something... you're just really focused on doing it, and not being distracted ... that concentration". (*Patient 1*)*

The reasoning of patients seemed to correspond with care providers' expectations, before the experiment (focus group 2), that LAKA might stimulate self-reflection and motivate behavioural adaptation by showing opportunity. After the experiment, care providers (focus group 3) emphasized the necessity of debriefing, for many patients, for transferring their experiences into desired learning results. Debriefing (group) discussions covered opportunity for patients to express experiences 'in' LAKA or 'to' LAKA. That is: vicarious experiences mediated by the avatar versus the non-mediated ones, such as declaring a lack of identification with the Avatar or the liking or disliking of entertainment-oriented features. Such non-mediated experiences were anticipated in focus group 1 when participants wondered, both critically and jokingly, why one would not just use anything else to trigger experiences as a basis for discussion (e.g., offering a piece of pie). After the experiment, care providers agreed that the best results are gained by addressing mediated as well as non-mediated experiences in debriefing, albeit depending on situational and patient needs.

*"Those mini-games in between, which ought to be less valuable: for reflection, you can get more out of that than from the encounters, because: I never go to Istanbul, and I do not like temples. So, I just clicked something. That mini-game is really stupid, I had to start all over again! You can reflect nicely on that … Why were you not interested in Istanbul? What does that say about you, your daily life, and your symptoms?" (*Health care provider*)*

6.4.2.3 Characteristics of intervention in context for triggering mechanisms (I/C+O)

Recipients made both positive and negative remarks about the serious gaming intervention. They agreed that learning mechanisms were compatible to other

educational and psychotherapy approaches in the rehabilitation programme. Two patients explained that the experiential learning opportunity supports learning transfer, which offers a relative advantage to regular text-based modalities. However, outcomes were regarded suboptimal due to the ambiguous and non-compelling provision of feedback. Other general barriers related to the limited duration, other design quality aspects, personalization or inflexibility of LAKA: response options were pre-programmed, valuable life domains and activities displayed may not be optimally personalized or exhaustive to suit individual patient's interests, too much time could be spent on 'non-active' elements, and a third (instead of first) person perspective was used, e.g.:

*"It (reflection) should be, as far as I am concerned, be more in the game and immediately after the choices you have made. Let consequences being 'lived through' and then get back on; if this, then what?" (*Patient 7)

*"The fact that all the answers that are given (options for responding in encounters) did not apply to me; I found that very difficult". (*Patient 5)

*"You are traveling the world, but it is actually about life. In that world you encounter something that you do not meet at home on the couch. In that journey you can put all kinds of aspects of life … Do you bring your partner? Are you going alone? Those are actually very essential choices. Why does that man (avatar) have to travel alone?" (*Expert)

Central planning of sessions by the clinic elicited varying views about the intervention, including the timing and presence of other patients in serious gaming sessions. One expert (focus group 1) expected it to be better when sessions take place within a short period of time (i.e., a maximum of 2 weeks). Recipients clearly preferred that debriefings took place shortly after playing. This could matter for 'confrontations' because memory recall on relevant serious gaming experiences gets more problematic over time. Some patients argued that serious gaming would have helped more in combination with previous programme elements when provided earlier. Others appreciated that gaming was not introduced earlier because its rationale would be more difficult to understand, or use of computer-based modality would be considered more

burdensome. One patient liked to have a debriefing with a care provider 1 on 1, while other patients found it interesting to hear about experiences of other patients, and to handle experiences with serious gaming (e.g., performing meditation) together in a room with other patients.

Care provider 2: *"In one scenario or one session, quite a lot happens: all the choices that people make. You could have concluded each session with an evaluation and reflect on what they just did. In the last session, it was not always clear what had happened and what they had experienced".*

When asking about potential patient factors before the experiment, care providers could only speculate about how complementary effects of serious gaming would depend on ongoing processes like restoring activities and social roles and pain acceptance, as they may vary strongly between patients throughout regular rehabilitation. After the experiment, both patients and care providers expected that a younger age, and possessing a habit or more self-efficacy regarding technology usage leads to more positive patient expectations and experiences. Patients who expected benefit from serious gaming explained this by the elicited awareness of dysfunctional cognitions, moods, or behaviours. Those with low outcome expectations, considered that emotional problems were absent or under control and prioritized other means for handling their (pain) symptoms (e.g., physical exercise) at that time. Providers expected that patients experiencing more difficulties and having a greater need for guidance in using LAKA (i.e., to get in control of their actions and transferring mediated experiences) could in fact be those who benefit the most. This seemed consistent with what patients admitted, albeit in lesser terms, e.g.:

*"When I first came there, and received such a tablet computer, games and such on computers really were not my thing. So, to me it was all 'abracadabra' what happened. I have been fighting with myself for the first 50 minutes; what am I supposed to do with this? And then you try something". (*Patient 5)

To care providers, patient expressions of difficulties encountered when using LAKA were useful input for debriefings. Care providers considered guiding patients for reflection to me more useful than facilitating convenience (e.g., offering

practical information and assisting with forgotten passwords, computer and internet settings, and game-controls). A care provider explained how (to prevent that) role performance in guidance could be influenced by an ambiguous attitude towards compatibility of computer-mediated learning and personal work style:

"I think our role is to say at the beginning: I am not going to tell you much. You get started, then I give information about how the device works, and eventually we will evaluate it … I must be self-critical: I was motivated to provide those sessions but sceptical, because games are not my thing. That is not good, because that influences your performance. Giving people little information has helped me not to be influenced". (Health care provider 1)

6.4.3 Serious gaming mechanisms and formal theory, and hypothesis formulation (step 2)

Regarding the particular way in which serious gaming may add to learning results, 'confrontation with oneself' could be identified as a necessary form of reasoning. Based on this finding, the (formal) self-discrepancy theory (SDT) was chosen as a suitable framework for understanding motivational and affective responses to serious gaming. Another advantage of this framework was its earlier application in research about psychological responses to videogames and about coping with chronic pain [327].

A first testable (alternative) hypothesis enabled to support or refute the idea that adding a serious gaming intervention adds to outcome changes during multidisciplinary rehabilitation, because it facilitates additional mindfulness changes:
The effect of serious gaming on patient outcomes, i.e. depressive mood, is mediated by change in learning results, i.e. mindfulness (hypothesis 1).

Qualitative findings did not provide clear reason to refute particular initial expectations about patient experiences that could qualify as serious gaming mechanisms for learning:

Sense of presence and positive affect are positively related to changes in learning results and health outcomes subsequently (hypothesis 2)

A third set of hypotheses concerned indicative testing of characteristics of patients for whom outcome changes attributable to additional serious gaming may be strongest. This firstly included the expectation of weaker game acceptance perceptions and outcomes in patients with a relatively higher adult age.

Moreover, health providers' description of patients who may perceived low ease in serious gaming whilst benefiting the most is typical for a coping style of infrequent problem-oriented or active coping. In a previous feasibility study with LAKA, control perceptions about serious gaming were found to mediate the positive relationship between active coping and usage intentions and frequency [218]. Therefore, we considered that learning results and subsequent health outcome changes attributable to serious gaming could vary with differences in levels of active coping of the patients.

Recipients also expected that LAKA does not directly nor explicitly target somatic symptom control and may therefore not be needed by patients who more strongly focus on pain control. Pain coping principally entails the quantity rather than the quality of a patients' coping with pain, and may not determine pain intensity levels [262]. This provided an explanation for a unexplained observation in the pilot phase: that CP patients with lower pain coping scores showed more frequent use of LAKA [218].

Finally, as LAKA was seen as a game that targets and 'confronts with' potential issues for emotional functioning, a difference between the experimental and control group in learning result and health outcome changes could exist depending on whether patients (still) had high levels of psychological symptoms before serious gaming. Patient factors were transformed into binary variables and added as moderators in moderated mediation models (see Appendix S2, table 2.9). The hypothesis tested by these models are:

Learning results and subsequent health outcome change, or game acceptance perceptions, vary with patient level factors, including age, coping (an active style, or focused on pain control), and present (psychological) symptoms (hypothesis 3).

Fourth, planning was considered to be a process of intervention delivery in context that could influence on game acceptance perceptions or learning at the level of the individual patient. Timeliness of debriefing was expressed in date

differences between a patients' debriefing and the last time that progress in LAKA was logged. Similarly, objective measures for the timing of serious gaming within the rehabilitation programme were calculated as date differences between intermediate outcome assessment and introduction to serious gaming, between introduction and debriefing, and between debriefing and post-treatment assessment. The structure of debriefing sessions attended by a patient was classified into 'group' (including 3 or more patients), or 'alone' (i.e., 1 on 1 debriefing by a care provider), as compared with a 'dyad' (2 patients were present). Although no explicit qualitative indications were found that differences in quality of delivery over time affect outcomes, patients' introduction session dates could indicate this.

Outcomes (learning results and or subsequent health outcome change) or game acceptance perceptions are influenced by variations introduced by central planning in timing of serious gaming sessions and structure of debriefing groups (hypothesis 4).

6.4.4 Quantitative analyses (step 3 and 4)

Figure 1 illustrates data-explorations for the triangulation of qualitative findings on ICMO's: Means with (bootstrapped) 95% confidence intervals are presented for mindfulness and depression (by group and time) across different sub-groups of patients. The sub-groups are defined by different configurations of patient and intervention characteristics in context. Figure 2 presents post serious gaming acceptance ratings for these same subgroups. These explorations show quantitative indications for ICMOs that correspond with qualitative indications: steeper changes in mindfulness and depression scores, or more stable acceptance levels in more favourable conditions (of I in C).

Legend for figure 1 and figure 2:
- IC (patient): a patient in this subgroup is at most 45 years of age, reported 'high' pre-levels of psychological symptoms compared to a 'normal' population, and had no 'high' levels of active or pain coping.
- IC (intervention): characteristics of intervention delivery in context for a patient were: received debriefing in a group within four weeks after introduction and at most 2 days after playing LAKA when it was completed for at least 50%.
- The width of the 'violins' represent numbers of observations across levels of serious gaming acceptance.

Figure 1: Outcome changes by patient and intervention delivery characteristics

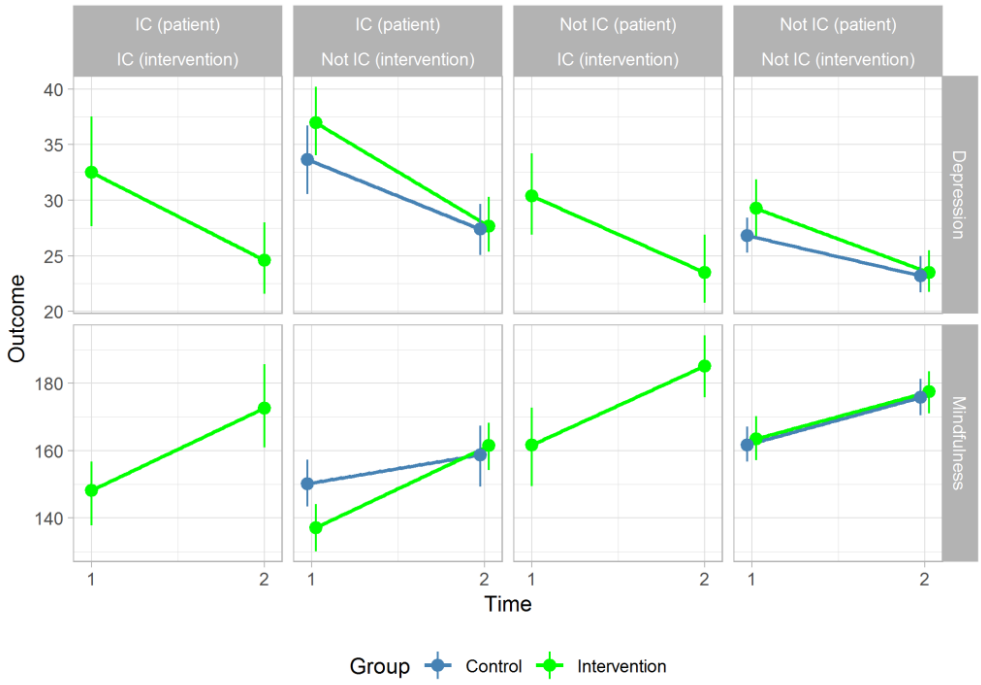
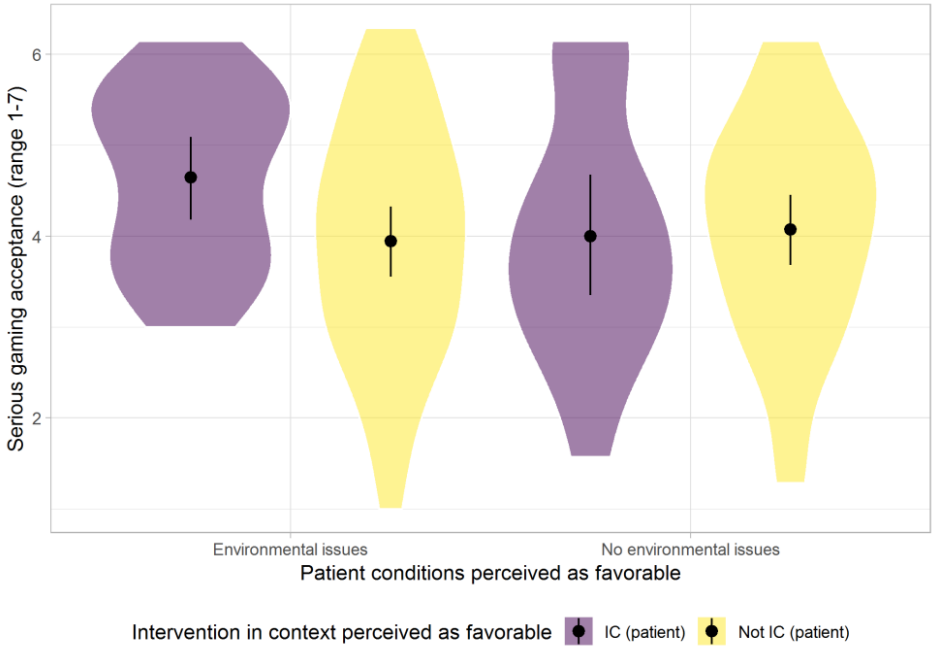


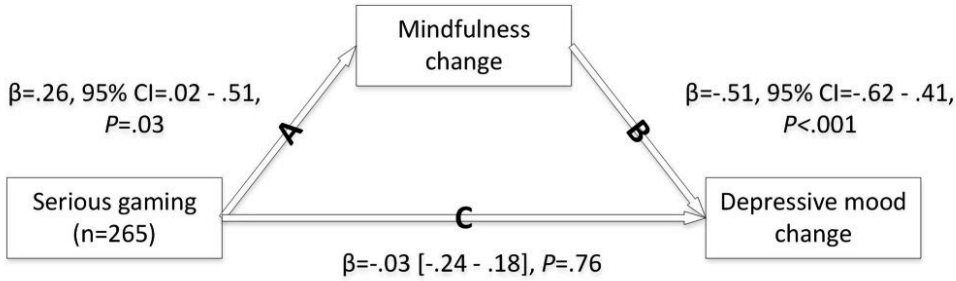
Figure 2: Gaming acceptance ratings by patient and intervention characteristics



6.4.4.1 The effect of group on health outcomes mediated by mindfulness (hypothesis 1)

In line with the first hypothesis, analyses showed that very small average difference in depression changes (dependent variable) (β=-.14, 95% CI=-.27 - -.02) between the serious gaming and control groups (independent variable) were mediated by a small average difference in mindfulness (mediator). Figure 2 presents regression coefficients for the effect of study group on mindfulness change (A-path), of mindfulness change on depressive mood change (B-path), and of study group on depressive mood change after controlling for mindfulness change (C-path). Similar results were obtained on fatigue (CIS-fatigue scale as dependent variable; β=-.15, 95% CI=-.29 - -.01) and current pain (0-100 numerical rating scale; β=-.09, 95% CI=-.19 - -.01).

Figure 2: The mediated effect of serious gaming on depressive mood changes through mindfulness changes



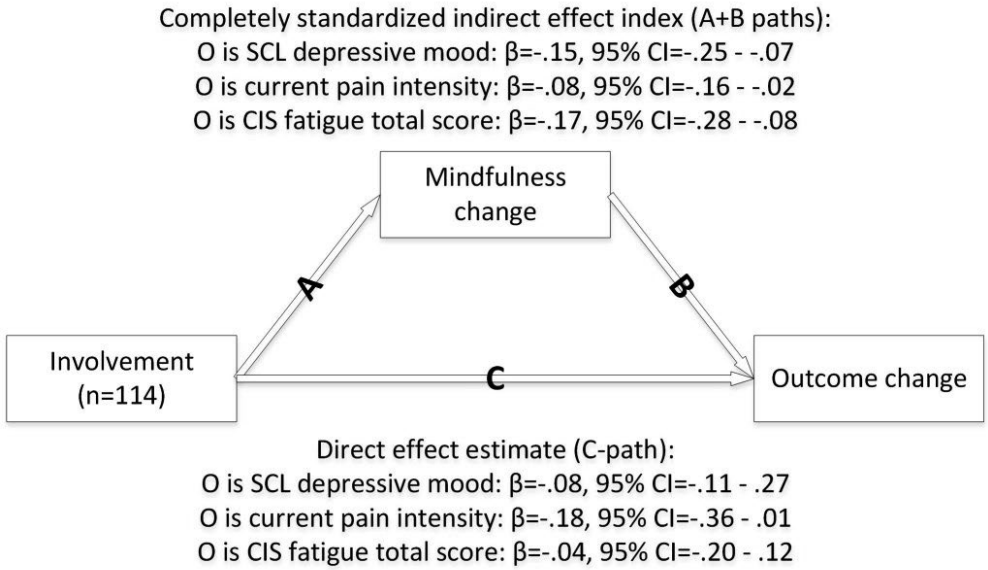
6.4.4.2 Relationships between serious gaming experiences, learning, and health change (hypothesis 2)

The calculated parameters of association amongst sense of presence (involvement and realism) and positive affect levels after serious gaming and mindfulness change only involvement showed a statistically significant and positive estimate.

Specifically, mean levels for affect valence after serious gaming were 3.00 (SD=.91, range 1-5) for positive and 1.53 (SD=.63, range 1-5) for negative. Mean levels for sense of presence sub-scale scores for intervention group participants were 2.59 (SD=1.29) for involvement and 2.40 (SD=1.05) for realism. Inter-correlations between positive affect, sense of presence, and game-acceptance were of moderate sizes (.57<ρ<.59, *P*<.001). Multi-linear regression of residual 'mindfulness' change scores on positive affect, negative affect, involvement,

realism, and outcome expectations (control variable) designated involvement as the only statistically significant factor (N=113, R^2=.10, β=.36, *P*=001). Figure 3 presents indirect (A*B path) and direct effect (C-path) estimates of mediation models with standardized residual involvement score (after regression on the other 4 predictors) as the independent variable, change in mindfulness as the mediator, and residual change in health outcomes as the dependent variables.

Figure 3: The mediated relationship between involvement and health outcome (O) change through mindfulness change



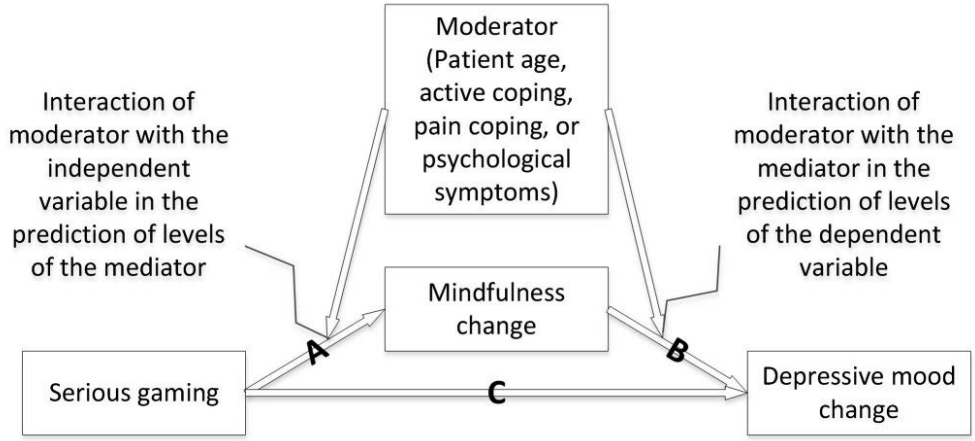
6.4.4.3 Differences in intervention effects on outcomes by patient factor (hypothesis 3)

Indications of varying game acceptance perceptions or learning results and subsequent health outcome changes by different levels of patient age, active coping, pain coping, or psychological distress are given by Pearson correlations between continuous patient factors and game acceptance perceptions, or adding dummy recoded patient factors as moderators in the previously fitted mediation model for depression (as illustrated in Figure 4).

Only age appeared to be was statistically significantly (*P*>.05) associated with game-acceptance levels (ρ=-.21, *P*=.03). No statistically significant parameter

estimates for moderated mediation (i.e. for A or B paths) by higher than average patient age (>45) were observed.

Figure 4: Model of indirect group effects conditional on patient factors

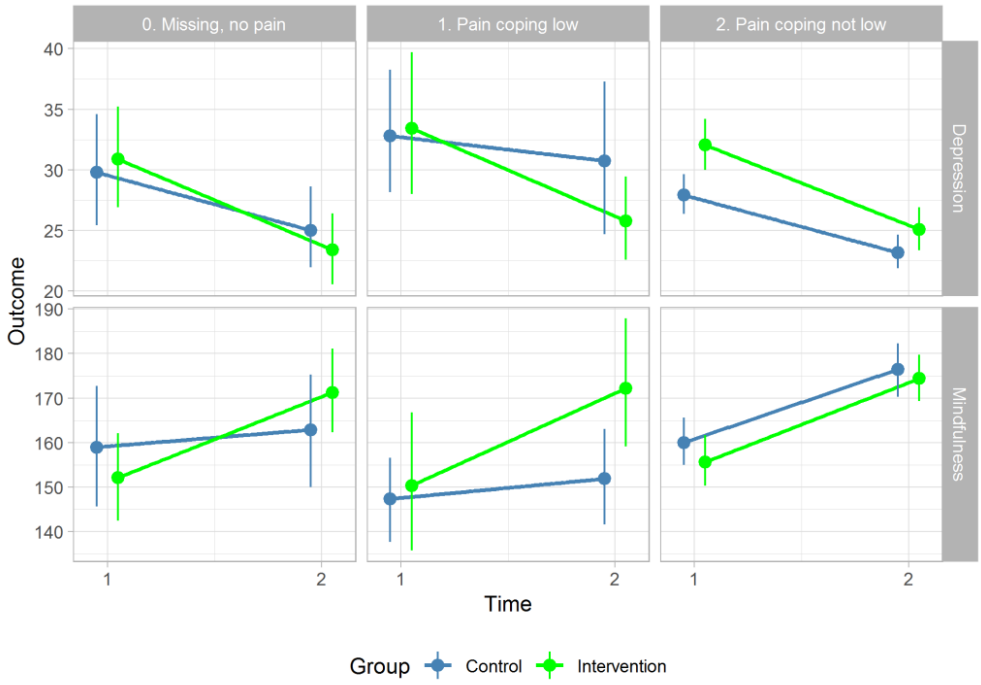


Moreover, a stronger average indirect effect of study group on health outcome change was seen in participants with 'low' or 'average' rather than 'high' active coping. Results are inconclusive about whether this is due to stronger intervention effects on mindfulness change in these patients, a stronger relationship between mindfulness and depression changes, or both. For absence of high active coping scores (<21, n=213/265, 80.4%), the moderated mediation index amounted -.26 (95% CI=-.06 - -.52) with β=.56 (95% CI=-.05 – 1.17) for the A-path, and β=-.31 (95% CI=-.01 - -.61) for the B-path. These, however, were subsequently β=.63 (95% CI=.02 – 1.24) and β=-.16 (95% CI=-.46 - .14) after removing a (bivariate outlying) case.

Furthermore, stronger indirect intervention effects were seen amongst participants with low pain coping (at t1). Learning result changes and the negative relationship between learning results and depressive mood were particularly weak in the group of participants with low pain coping who did not receive additional serious gaming. Within the sub-group of 33/214 participants with pain coping scores of Z<1 (18/121 from the intervention group and 15/93 control group), the indirect effect estimate (β) was -.79 (95% CI=-1.50 - -.31) higher than within the 181/214 other participants. Estimates of interaction effects with A and B paths were subsequently β=.85, 95% CI=.12 - 1.59, and β=-.47, 95% CI=-.80 - -

.13. Figure 5 visualizes the average mindfulness and depression changes (with bootstrapped 95% confidence intervals) over time by the study groups between levels of pain coping.

Figure 5: Group differences in average depression and mindfulness changes by pain coping



Finally, it was observed that in patients with high or very high psychological symptoms as compared to low or average levels before serious gaming, associations between mindfulness and depression changes were stronger. This did not imply a moderating influence on the indirect effect of serious gaming. Specifically, for SCL total scores >132 (i.e. high or very high as compared to the means within a sample drawn from the general population), a moderation effect was observed only for the B-path: β= -.58, 95% CI=-.81 - -.35). No different overall indirect effect estimates were seen between the sub-groups (index of moderated mediation=-.19, 95% CI=-.40 - .02).

6.4.4.4 Differences in outcomes by intervention in context (hypothesis 4)

Finally, the results partly agree with the hypothesized differences in game acceptance perceptions or learning result and subsequent health outcome changes by planning related differences in circumstances of serious gaming intervention for patients: the timing of sessions within the programme, debriefing group structure, and timeliness of debriefing after play.

Multi-linear regression models showed that none of the objective indicators were statistically significantly associated with health outcome changes. For mindfulness change, model prediction only improved by the addition of the dummy variables for debriefing session structure (n=142, R^2_{change}=.05, *P*=.03). This was accounted for by the dummy for group structure (more than 2 patients were present): b=.43 (SE=.19, *P*=.02). Generally, addition of timing variables did not improve the mindfulness change model (n=142, R^2_{change}=.05, *P*=.078), but statistically significant parameter estimates were seen for the date differences between introduction and debriefing (b=-.02, SE=.01, *P*=.03) and between debriefing and post-treatment assessment (b=-.02, SE=.01, *P*=.02). Regressing game acceptance perceptions on the dummy coded difference between last day of playing LAKA and debriefing also resulted in model improvement (n=112, R^2_{change}=.09, b=-.73, SE=.22, *P*=.001).

Thus, mindfulness changes were higher for patients who attended debriefing in a group and completed serious gaming sessions in relatively quick succession and late in the rehabilitation programme. Moreover, when time between playing LAKA and debriefing attendance was not very short (more than 2 days), average game acceptance perceptions were estimated to be 0.7/7 lower.

6.4.5 Mixing the qualitative and quantitative results (step 5)

Two original ICMOCs were constructed by updating initial formulations on the basis of the qualitative and quantitative results (See textbox 2). The construction of transferable programme theory through comparison with previous research, including formal theories, is presented in the discussion.

Textbox 2: Final configurations of contexts, mechanisms, and outcomes

ICMOC 1: Acceptance perceptions after serious gaming (feasibility mechanism or context for learning and health outcome change) are lower when:

- design qualities with respect to feedback and adaptation to recipient preferences are limited (I in C);
- the patient who uses it is of an older age (C), and;
- implementation processes (i.e. central planning) within responsible organizational units do not consistently facilitate immediate debriefing after play to avoid forgetting meaningful experiences to share (I in C)

ICMOC 2: Additional self-awareness in daily life (rehabilitation mechanism or serious gaming outcome) and subsequent health outcome changes (rehabilitation outcomes) are influenced by serious gaming tasks that elicit patient awareness of discrepancy between self-scripts and actual selves and their emotional consequences (serious gaming mechanisms) when:

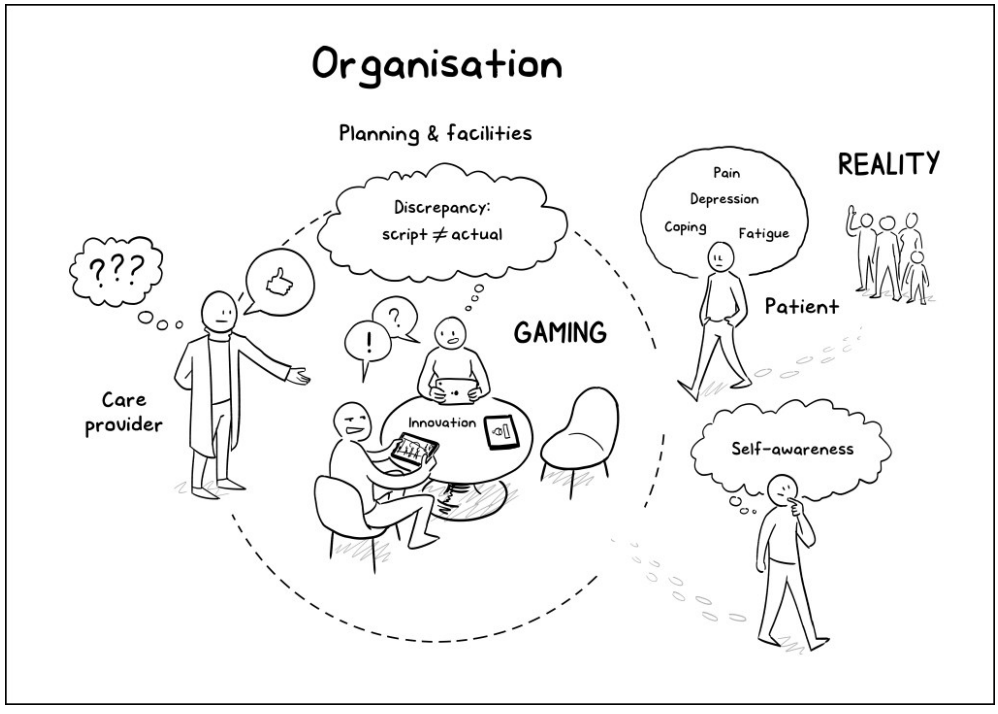
- it constitutes an innovation that is relatively advantageous (i.e., for experiential learning) and compatible with a larger treatment programme (i.e., its rationale) (I in C);
- the patient has low inclination for active coping with stress or pain coping (using various ways to control it) (C2) and;
- organizational implementation processes are characterized by adequate planning for the patient: sessions are facilitated to address a timely need and debriefing is followed with in a small group with other patients (I in C)

6.5 DISCUSSION

6.5.1 Summary of findings and comparison with existing literature

This study aimed to inform policy makers and care providers interested in implementing serious gaming in actual contexts of health care. Hereto, it looked into how, why, for whom, and when facilitating additional serious gaming during multidisciplinary rehabilitation could be effective for patients with CP or FSS. To this end, the serious game LAKA and its processes of influence on learning and health outcomes were qualitatively and quantitatively investigated. Explanatory aspects that are considered least uncertain after this study are given in the form of programme theory, which is depicted in Figure 5. In the following sections, this final programme theory discussed after summaries of findings that highlight areas of support, refutation, refinement, and extensions of initial programme theory, and comparisons with previous research (per research question).

Figure 5: Programme theory of serious gaming during the multidisciplinary rehabilitation of patients with complex CP or FSS



6.5.1.1 How serious gaming affects outcome change during multidisciplinary rehabilitation

Addressing the 'how' question entailed (1) asking patients about how introducing serious gaming during multidisciplinary rehabilitation could influence health change, and (2) estimating how much variation in learning result and health outcome changes were attributable to (distinctive experiences) of serious gaming.

Firstly, initial expectations were supported by the consistent qualitative and quantitative indications that serious gaming, when it contributed to rehabilitation outcomes, elicited patients' heightened self-awareness in situations of daily life in ways, which could help to reduce depressed mood. The present study tested the same mediation model as in a previous meta-analytic study [328]. Both studies suggested a very small indirect average effect of mindfulness-based intervention on mental health outcome changes through small intervention effects on mindfulness skill. However, quantitative results in this study differed regarding the absence of a significant direct intervention effect. The meta-analysis included

mostly comparisons of comprehensive mindfulness programmes with passive control conditions whilst the comparison group of the present study followed an active multidisciplinary rehabilitation with various other face-to-face delivered techniques (e.g., neuroscience education, cognitive restructuring). Therefore, outcome changes in our study may be affected already by those other elements. Finally, the finding that learning result, but not health outcomes, decreased with time between debriefing and post-treatment could reflect limited sustainability of behavioural change effects [30].

Secondly, the findings of this study suggest a specific refinement regarding how serious gaming strengthens learning: behavioural change techniques implied by the tasks of LAKA triggered a productive form of patient 'reasoning' referred to as 'confrontations with oneself'. Furthermore, participants agreed with the initial expectation that debriefings can facilitate transfers of individual experiences to learning results for daily life [104, 242, 251]. Herein, an unexpected result was that care providers saw learning opportunity in patients' difficulty to engage in (unknown experiences of) serious gaming. Furthermore, neither positive affect nor perceived realism during gaming appeared to relate to learning or health changes in a direct and simple (linear) way. However, the findings did support that patient sense of involvement (i.e., attention devoted to the virtual environment) during serious gaming, which was at a high level as in other immersive technologies, strengthens learning and health outcome changes. This mostly resonates the proposition from previous work of positive moderation by high involvement of behavioural change effects of games as compared with other modalities (e.g., text-based web-pages) [329-332]. The findings leave room for other explanations, including that pain intensity could be influenced by involvement in virtual environments through distraction [180].

6.5.1.2 Why serious gaming affects outcome change

Awareness of discrepancies between 'actual-selves' and 'self-scripts' may be a good way to conceptualize the necessary trigger for learning from (mindfulness-based) serious gaming. Textbox 3 explains SDT and how it was previously used in research on coping with chronic pain and individual responding to computer games. SDT complements the S-ART model of mindfulness mechanisms [42]. Mindfulness can be seen as an adaptive way of processing self-discrepancies to

moderate affect and social behaviours [42, 333]. From an SDT perspective, a focused attention (meditation) exercise instruction includes: ('gently') returning focus of attention to a chosen (ideal) mental or sensory object when the present (actual) object of attention deviates (is discrepant) from that goal state. In this respect of mindfulness change, the type of reasoning triggered by LAKA might differ from that of health behaviour games aimed at changing specific cognitive antecedents of health behaviours, but explanations (i.e. involvement) for quality of learning clearly coincide [332].

Textbox 3: The basics and relevant applications of self-discrepancy theory

The basis of self-discrepancy theory (SDT)

SDT predicts particular affective states (e.g. dissatisfaction, disappointment, agitation) from degrees of discrepancy between a person's 'actual' self-state and a self-script ('ideal' or 'ought to' states from own or others' perspective) [327].

SDT in literature on coping with chronic pain

Self-discrepancies are prevalent in both depression and CP, which often co-exist [214, 334]. When pain (or fatigue) symptoms become chronic, self-scripts conditional on the absence of those symptoms may be a source of emotional disturbance (and maladaptive activity patterns) [5, 214]. SDT was used to predict functional improvement in CP patients by motivating pursuit of possible selves and perceptions such as interest, approval, or acceptance that are not actually conditional to physical symptoms [335].

SDT in literature on individual responses to computer games

Previous research showed that perceived opportunity for realizing ideal-selves in computer gaming especially motivates individuals with larger actual-ideal self-discrepancies [206]. Other studies went into detail about how games and playing conditions can elicit the desired responses. A crucial property for influencing self- or emotional regulation processes with games is user identification with avatars in storylines [336]. Herein, avatars have (anti-)heroic qualities and challenges (e.g. growing, defeat an antagonist, etc.). In LAKA, the avatar journeys start in a state of discrepancy with respect to a relevant goal or ideal, and is committed to change. Users are then given control over avatar behaviours related to the goal state. However, it is not self-evident that new capacities for achieving goal states transfer from gaming worlds into 'reality'. This could depend on social interaction in the context of use [245]. Finally, findings of the present study corresponds with a previous study that discovered positive behavioural change effects by eliciting self-discrepancy in videogames when users are primed to self-regulate with a prevention instead of a promotion focus [337].

6.5.1.3 For which patients does serious gaming affect outcome change

Initially, there was much uncertainty about for whom (i.e. which patients with CP or FSS) the present serious gaming intervention would be more or less effective. The findings of this study enabled to propose extended programme theory about for whom serious gaming intervention could be more or less feasible or effective: (1) its acceptance is weaker in patients with a relatively higher age, and (2) its contribution to learning and health outcomes is stronger (i.e. lagging change is compensated for) in patients who perceive less control over stress or pain. Both qualitative and quantitative results suggested more appropriate chances for a meaningful effect of serious gaming on depressive symptoms in patients with less active (with regard to stress) or varied (with respect to pain) coping styles. In an identifiable subgroup of patients, the average effects may be 'small' or 'medium-sized' instead of 'very small' as found for all the patients [297]. The suspicion rises that the serious gaming could be especially productive for patients with characteristics that predict fewer benefit from usual treatment activities. At the same time, serious gaming can be questioned for its effectiveness for patients with a tendency to display frequent active or pain coping.

These findings connect to previous work. Associations between age and technology acceptance have been inconsistent across contexts of use [190]. Previous pilot results provided an explanation in lower perceived ease in older patients due to anxiety or low self-efficacy regarding the use of technology [218]. Contextual influences could be cultural reinforcement of associations of gaming with young peoples' skills or social comparison between early and late adopters of technology. With regard to relevant coping differences for patient outcomes, it was previously found that 'active' or 'problem-oriented' coping and pain coping are both characterized by control appraisals and positively related to health outcomes in patients with CP [9]. Improvement of mindfulness (through acceptance of aversive experience, emotional regulation, perceived support) can enhance adaptation to CP (e.g., moderate depressive symptoms) independently of pain control appraisals [338-340]. Furthermore, a mindfulness approach, not serious gaming in particular, may be more effective in patients who have more to gain with respect to emotional functioning [27, 305].

6.5.1.4 When serious gaming affects outcome change

Other conditions for effects of serious gaming during multidisciplinary rehabilitation on patients with CP or FSS were studied by looking at characteristics of innovation, care provider, and organizational context factors in the study setting. In this regard, it is proposed that blended serious gaming intervention triggers additional productive reasoning when providing (1) a relatively advantageous mode (i.e., with experiential features) and (2) valid and compatible treatment approach (i.e., mindfulness-based), implemented with (3) high fidelity with respect to processes of session planning and facilitation, including a group-based debriefing. Moreover, patients may have more positive perceptions of their usage of serious gaming intervention when adapting better to recipient needs and preferences. Tight planning for immediate debriefing after play may also help in this regard.

The identified contexts in which serious gaming was found to be more acceptable and effective connects to previous studies. The importance of adopting a valid rationale in developing games for health was emphasized in existing guidelines [254]. The possible relevance of group dynamics in effective debriefings were touched upon [251]. Our findings resonate those of a previous implementation study of internet-based cognitive behavioural therapy in which adaptability was identified as an important innovation level barrier for usage [341]. The indicated importance of timely face-to-face interactions agree with the notion that debriefings are necessary for generally satisfying learning experiences after serious gaming [251]. Care providers' compliance and slightly changing scepticism about serious gaming agree with previous findings on care provider perspectives on digitalized interventions, including serious gaming, for mental health improvement [342, 343]. Clearly, the proportions of patients that logged in for using LAKA at least ones, amongst study participants and eligible patients that had the opportunity to do so, were much higher under the circumstances of this evaluation study (155/156/171) than in the previous feasibility pilot (71/116/410): when serious gaming was available only for one computer platform, was not an embedded treatment component, and did not include care provider support [218]. Under those 'non-committal' circumstances, usage may be less well explained by a process of 'going with the flow', and more so by individual planning processes [188, 344].

6.5.2 STRENGTHS, LIMITATIONS, AND FUTURE DIRECTIONS

Key strengths and limitations coincide with how realistic approaches to process evaluation were applied. To realists, various research methods are commensurable and complementary and none is generally preferable in support of programme theory development [345]. (Randomized) controlled experiments provide precise estimates of outcome attributions to experimental conditions, but do not provide new insights on generative causal mechanisms [346]. Therefore, embedded experimental mixed-methods ideally suited the questions and approach of this study [347]. Qualitative methods served to refine and extend initial insight on generative causal pathways, and quantitative methods enabled to triangulate and test hypotheses on indicative observable consequences of those insights: statistical parameters for outcome changes, patient experiences, and moderating patient or intervention factors. In this way, the study adds to previous (sparse) examples of quantitative research within a realistic paradigm, including (Bayesian) multiple regression, structural equation modelling, latent variable analyses, and propensity score methods, [348-350]. However, qualification of this study as 'realistic' may be limited by the late adoption of its principles within the project. This could have influenced initial programme theory formulations (e.g. conflation of intervention characteristics with mechanisms in the protocol stage) and, therefore, possibly, also the data collections [273]. Ongoing future improvement of theoretical and contextual approaches to evaluating impact of (digital) innovation of biopsychosocial and mental health treatments is suggested (as motivated in Textbox 4) [25].

Textbox 4: Considerations for realistic eHealth effectiveness research in related fields

Lacking explanations for heterogeneous outcomes of interventions targeted at CP and FSS patients may reflect 'complexity' [345]. Treatment targeting and tailoring decisions relies on limited evidence and consensus building [351]. Therefore, several researchers suggested that empirical evaluations should emphasize more on contextual sensitivity and theory development for gaining transferable insights into relationships between components, mechanisms and actual conditions of biopsychosocial treatments [27, 82, 305, 352, 353]. Similar questions are to be answered in support of integrating eHealth into complex routine health services [247]. As RE specializes on these areas, it could inspire methodological advancement in support of important new insights for programme quality improvement, treatment allocation decisions, personalization, and expectation setting for patients.

General strengths and weaknesses of the mixed-methods design were previously reported [273, 297], but particular strengths and limitation of its execution are noted here. First, transferability is supported on a theoretical level by the RE approach, and strong representativeness was achieved by the sampling of the patients. However, only a single setting was investigated wherein contextual factors had limited variation. The disaggregation to individual level does not reflect a broad range of variation in interventions and contexts across possible social environments of patients, care providers, treatment centres, and country settings.

Secondly, internal validity varied across study objectives and corresponding programme theory elements. As the study protocol had to be ethically approved before data collection started, quantitative measure selections could not be based on updated expectations after qualitative investigation. In RE, as in any other methodological approach, data collection decisions are ideally informed by the most recent state of theoretical insight.

Thirdly, one may question (in retrospect) if late adoption of RE within the project limited the qualitative data collections or not, as broad sets of potential explanations adequately represented the status of literature. Perhaps, more elaborate initial theoretical development could have enabled to (1) pose more or better follow-up questions to participants during interviews (e.g. for differentiating contexts and mechanisms between acceptance and learning), (2) narrow sets of sensitizing concepts and topics, (3) or determine more specific criteria for data saturation. Trustworthiness of the qualitative data is supported by some techniques (i.e., part of the qualitative data was independently coded).

Fourth, there were particular strengths and limitations to the quantitative methods. To reduce risk of capitalizing on chance for finding statistically significant results, the number of hypothetical factors was strongly reduced by embedding qualitative analyses before outcome inspection (see trial register) and performing sensitivity analyses on key quantitative findings. Similar results were obtained when estimating mindfulness changes over time between the intervention and control groups with a mixed linear modelling approach with corrections for potential confounding factors (See S2 Appendix, Table 2.10). A limitation is that the pre-calculations of the sample size were based on modelling outcomes with a few covariates, but did not specifically anticipate the testing of 'moderate mediation hypotheses' or more complicated (configurational)

propositions. Furthermore, criteria for hypothesis rejection were not corrected for multiple hypotheses testing. Psychometric qualities of the mindfulness measurements available for this study were rigorously assessed by an independent testing institute, but not by the peer review process of an international scholarly journal. The study protocol did not completely rule out degrees of freedom in selecting and calculating quantitative measures. Therefore, the findings of this study are to be interpreted in the light of theory development and informing future tests of plausible (realistic) propositions with newly collected data and complementary methodological strengths.

6.5.3 Conclusions and recommendations

Inspired by a realistic approach, this study started with selection of potentially relevant theories and ended with an integrated fallible model [346]. Serious gaming (i.e. a 4 hour intervention during an intensive multidisciplinary rehabilitation programme) may facilitate reasonable additional chances for reduction of emotional symptoms in CP or FSS patients with low control appraisals of their current stress or pain, due to the triggering heightened attention and improved awareness of self-discrepancies. This opportunity could further depend on adequate implementation processes for timely planning and facilitating of professionally guided exchange of experiences between patients. At the same time, clinically relevant effects of serious gaming intervention may be unlikely in other patients and lesser circumstances.

This timely programme theory already offers some transferable insights and guidance (principles and demands) for patients, care providers, health care organizations, insurers, national policy makers, and businesses who will take future decisions on sustainable future implementation of serious gaming. It may not be wise to offer this form of serious gaming, with a similar (late) timing during rehabilitation, to all patients: including those appraising that their stress and pain are (already) under control.

Realizing the promise of serious gaming benefits from ongoing effort to support, refute, refine, and extend programme theory. In doing so, focus should be guided by important stakeholder perspectives. It is recommended to extend the scope of programme theory to the outcome domains of patient quality of life,

organizational adoption and implementation, and cost-effectiveness. Mechanisms of learning from serious games could be formalized with refined prospective studies, i.e. applying SDT to construct predictions on how cognitive and emotional consequences vary with specific changes in serious gaming designs and contexts. Finally, investigations could zoom in and out on micro (e.g. technical) or macro level (e.g. organizational) conditions for serious gaming with impact. For example patients and software developers and data-scientists could participate in understanding and optimizing software adaptation (e.g. patient feedback) to recipient characteristics for learning and health improvement [319]. Care providers could be involved in optimizing feedback provision (e.g. incorporating the use of log-data) and fit with work routines. And lastly, on an organizational or societal level, policy makers could participate in theorizing on preconditions such as financial arrangements and dissemination platforms.

Abbreviations:

- **CP:** Chronic Pain
- **FSS:** Functional Somatic Syndrome
- **ICMOC:** Intervention, Context, Mechanism, Outcome Configuration
- **RE:** Realist Evaluation

7 GENERAL DISCUSSION

Should games for health be judged, hyped, or taken seriously?

A game scenario

After a child in the queue in front of the museum (London Tate) had emptied his cup of juice over your pants...

Mother: "Oh, I'm sorry."
Avatar: "Oh!
Mother: 'Do you want a cloth?'
Avatar: “Thank you”
Mother: 'I thought: would I take them to the museum?'
Avatar: "In any case better than a video game."
Mother: "Oh, but there are good video games as well, nowadays. The kids can learn a lot from it. Us too by the way, big people... "

Avatar:
Option 1: "I still have to come across the first educative video game."
Option 2: "But all those hours in front of a screen, that can never be good?"
Option 3: "Maybe, but there is still nothing like real art."
Option 4: "I dare to hope, madam."
Option 5: "Oh that interests me. Do you know a few titles?"

After options 1-4. Mother: "Times are changing, sir. Come Ilya ...”
After option 5. Mother: 'Give me your e-mail later, then I will forward them.'

7.1 BACKGROUND

To cope with persistent somatic symptoms and to reduce consequential burdens of functioning, patients can benefit from the skill to be 'mindful': a temporary non-judgmental, non-reactive and present centred state of attention and awareness [19, 42]. Training this skill, like identifying and changing particular dysfunctional cognitions and behaviours, is an efficacious strategy in biopsychosocial management of chronic pain (CP) or functional somatic syndromes (FSS) [127, 290]. Biopsychosocial approaches, like multi- or interdisciplinary rehabilitation programmes, can be cost-effective treatments [26], but it was estimated that out of 1 in 5 Europeans with moderate or intense pain that persisted beyond 6 months, nearly half received inadequate treatments [57]. For chronic low back pain only, which is the most common CP and FSS condition, the sum of the direct health care costs and indirect costs of reduced daily functioning abilities could be larger than for any other health condition [294]. Not only better understandings of biological mechanisms of particular symptom patterns are needed [354], but also of what treatment delivery modes could be used to enhance the accessibility and financial viability of effective biopsychosocial approaches [60].

Computer technology, such as the internet and games, could offer advantages in increasing accessibility of efficacious behavioural change support, provider control over intervention content, improving convenience, and limiting costs (e.g., patients' travelling expenses, saving time of expert care providers) [355]. Serious (health) games can be a kind of computer-based intervention for both enjoyment and health improvement [242]. A new serious game, 'LAKA', was developed for being offered during a biopsychosocial multidisciplinary rehabilitation programme. The feasibility and effectiveness of doing so, as for serious games for health in general, requires rigorous validation [254]. Therefore, this thesis investigated influences of computer technology, including the internet and games, on the effectiveness of behavioural change support in biopsychosocial treatment. The following questions guided the research:

Research question 1: To what extent (in what respect and for how long) are computer-based behavioural change interventions effective for patients with complex chronic somatic symptoms? This question includes:

To what extent (and in what respect) is multidisciplinary rehabilitation with serious gaming effective as compared to multidisciplinary rehabilitation without serious gaming?

Research question 2: Why and for whom is Serious gaming feasible, i.e. demanded (accepted and used) and implementable, as a complementary intervention during the multidisciplinary rehabilitation of patients with complex chronic somatic symptoms?

Research question 3: How, why, for whom and when are computer-based behavioural change interventions effective in patients with complex chronic somatic symptoms? This includes:

How, why, for whom and when is multidisciplinary rehabilitation with additional serious gaming effective as compared to multidisciplinary rehabilitation without serious gaming?

To examine these questions, steps were taken as recommended by the medical research council guidelines for evaluating complex interventions [47]: from development of the serious game 'LAKA', to examination of its feasibility in a pilot, and evaluating effectiveness with respect to health outcome change. Mixed-method designs were used in all stages of empirical evaluation. Before and during empirical investigations on serious gaming, methods of systematic reviewing and meta-analysis were applied on previous experimental studies of computer-based interventions for patients with functional somatic syndromes or chronic pain. This provided a base for comparison between the experimental findings of ourselves and others. Towards the end of research, process evaluation increasingly took a contextual sensitive and theory oriented, or 'realistic', approach [255].

This discussion chapter first presents a summary of thesis findings and reflections for each of the three major research questions. Secondly, methodological considerations and suggestion for future research are described. Thirdly and finally, implications and recommendations are given for policy and practice with a focus on implementation of computer- and game-based interventions on a larger scale, which is a presumable next step after outcome and process evaluations.

7.2 SUMMARY OF THE FINDINGS AND REFLECTIONS

7.2.1 The degree to which computer- and game-based interventions are effective

Literature about the effectiveness of computer-based interventions in general was comprehensively studied. Within this broader context, empirical findings about the effectiveness of serious gaming during multidisciplinary rehabilitation could be placed.

7.2.1.1 Effectiveness of computer-based interventions in general

By means of the systematic review and meta-analyses (chapter 2), it was found that computer-based interventions likely result in small and sustainable effects on physical and emotional functioning in patients with complex chronic somatic symptoms, but not under all circumstances. Previous work was complemented with efficacy estimations from larger pools of studies, distinguishing between several health outcome domains and assessment periods. Moreover, it was considered that the type of comparison chosen by experimenters is a methodological choice that reflects the kind of health care context to which findings are plausibly transferable. Experimental results obtained after comparison with 'passive' situations as control conditions, such as waiting-list, usual or standard care (by a general practitioner only), 'attention placebos', or provision of information only are considered to inform about effectiveness when the computer-based intervention is the only option for receiving biopsychosocial intervention. Mindfulness or cognitive behavioural therapy strategies, for example, are not accessed by any other means. Effectiveness of computer-based interventions may be something different when it is a substitute or complement for biopsychological interventions that *can* or *are also* accessed by other means. Effectiveness may then be indicated by the results of comparisons with 'active' control conditions, including different versions of computer-based intervention (e.g., one that adopts a different strategy or adds the use of short message services for reminders), face-to-face intervention of similar content and intensity, or a biopsychosocial programme without additional computer-based component.

In comparison to passive controls, the estimated average benefits of computer-based interventions were found to be of a 'small' or 'medium' size. This means clinically important to part of the patients. This was a solid result with respect to outcomes in domains of emotional functioning (i.e., depressive mood) or

catastrophic thinking (i.e., or other kinds of coping or cognition like acceptance or self-efficacy). Effects on symptom severity, quality of life and functional interference were found to be equally strong on average, but the substantial heterogeneity between studies required further examination of differences between interventions, patients, or settings (e.g., outcome measures).

In comparison to active controls, computer-based interventions were not found to be effective, or only to a very small extent. For this comparison, meta-analyses found 'very small' effects on functional interference or catastrophizing outcomes, and no effects on symptom severity and depression outcomes. Although studies were not numerous enough and too heterogeneous for drawing firm conclusions at this time, it seems unlikely that better outcomes after biopsychosocial treatment will generally result from adding computer-based behavioural change support. At the same time, outcomes after computer-based or face-to-face group therapy of similar intensity and content may be equal.

7.2.1.2 Effectiveness of serious gaming during multidisciplinary rehabilitation

The results of a natural quasi-experimental design (n=275) (chapter 5), suggested that an additional (mindfulness-based) serious gaming intervention (with LAKA), during a biopsychosocial multidisciplinary rehabilitation programme, resulted in a 'very small' complementary effect on physical and emotional symptoms. By using a mixed-linear model, marginally accelerating outcome changes were shown for the time interval that additional serious gaming was followed by the intervention group and not by the control group. In both study groups, the outcomes (pain intensity, fatigue, and psychological symptoms, and pain catastrophizing) generally improved throughout the rehabilitation programme to an extent that plausibly (not evidently) exceeded natural courses and effects of simpler treatments. Together, qualitative and quantitative findings pointed to a complementary function for reducing (depressive) mood, but not for pain catastrophizing. Interpretations of these findings suggested weaker effects than the small to medium effects that were previously found in meta-analyses on serious games for behavioural and mental health outcomes [30, 356]. Moreover, extraordinary results of a small early study (n=50, published in 2008) pointed out that aftercare via interactive voice response might be a better strategy for complementary computer-based intervention in multidisciplinary treatment [55]. Nonetheless, our findings hinted at the relatively little time that health care

providers needed for the delivery of serious gaming. Again, the suggestion of a positive effect of serious gaming during multidisciplinary rehabilitation agrees well to several other studies that indicated modest effects of computer-based intervention on selective outcomes in comparison to 'active' controls, including an experiment published after the final search for chapter 2 [357, 358].

7.2.2 Why and for whom serious gaming is feasible

By means of two subsequent mixed-method studies for examining intervention processes (chapter 3, 4, and 6), it was shown that serious gaming intervention is implementable and used by patients as a normal and integrated part of a regular multidisciplinary rehabilitation programme. After performing improvements in implementation, as suggested by patients in a pilot study, there were no indications that substantial groups of patients could or did not participate in the serious gaming intervention. Many patients did not engage in research participation or serious gaming in the pilot, when LAKA had been offered for usage at home without therapist support from the first week of the rehabilitation programme, because other efforts for the programme or personal issues were considered more urgent. Therefore, facilitating and investigating serious gaming at the clinic and at a later stage of the rehabilitation programme was more feasible.

By examining processes, it was shown that several factors mattered for patients' acceptance, or actual initiation or continuation of serious gaming:

- pleasure appeared to be the most consistent source of patient motivation for using serious gaming over time;
- a relatively higher (adult) age related to more initial hesitance or anxiety about using the technology and to experiencing more unease in use;
- higher perceptions of ease or internal control may explain why higher acceptance and frequency of using LAKA was seen in patients with more active coping styles;
- existing habit of using computers or games and provision of timely opportunity to discuss game experiences with a care provider resulted in better acceptance.

Furthermore, some barriers remained for serious gaming: it was impractical for patients with certain special needs, trouble for software access (i.e., handling password protection) could not be completely prevented, and some limitations

(i.e., regarding flexibility or personalization tailoring) were found to be inherent to the design of LAKA.

7.2.3 How, why, for whom and when computer- or game-based interventions are effective

Especially after contributions of both the literature study (chapter 2) and process evaluations (chapter 6) within this thesis, the following is proposed on how, and in what circumstances, computer- and game-based intervention influence upon patient health outcomes:

- computer- and game-based interventions can produce sustainable and clinically relevant improvements across domains of physical and emotional functioning of patients through their attentive use of cognitive behavioural change resources (how);
- because of changes in coping with bodily, personal, and environmental conditions (e.g., reductions in rumination, experiential avoidance) (why);
- in patients who experience uncontrolled sources of stress as a factor or consequence of a functional somatic or chronic pain syndrome (for whom);
- when the innovation includes truly relatively advantageous functions (not provided by any other means), including experiential learning or 'exposure' techniques, delivery modes that are preferred/selected by the patient and non-abundant, and guidance by professional health care providers (when).

7.2.3.1 Explanations of effectiveness of computer-based interventions in general

Our literature study hinted at what explanations exist for computer-based intervention outcomes. Classification of the intervention in behavioural change techniques disclosed frequent enclosure of mindfulness or cognitive behavioural change strategies of skills training (in meditation or relaxation for reducing negative affect), shaping knowledge, and problem solving. This indicates that the modest improvements in patient emotional functioning may be generally explained by how patients learn to adapt by using such content to reduce negative affect, refute or defuse catastrophic thought, or increase acceptance.

Furthermore, meta-analytic sub-group analyses suggested intervention or patient characteristics that could account for variation in effects on somatic symptom, quality of life, or functional interference. Better effects on somatic symptom outcomes were found for interventions that included guidance by

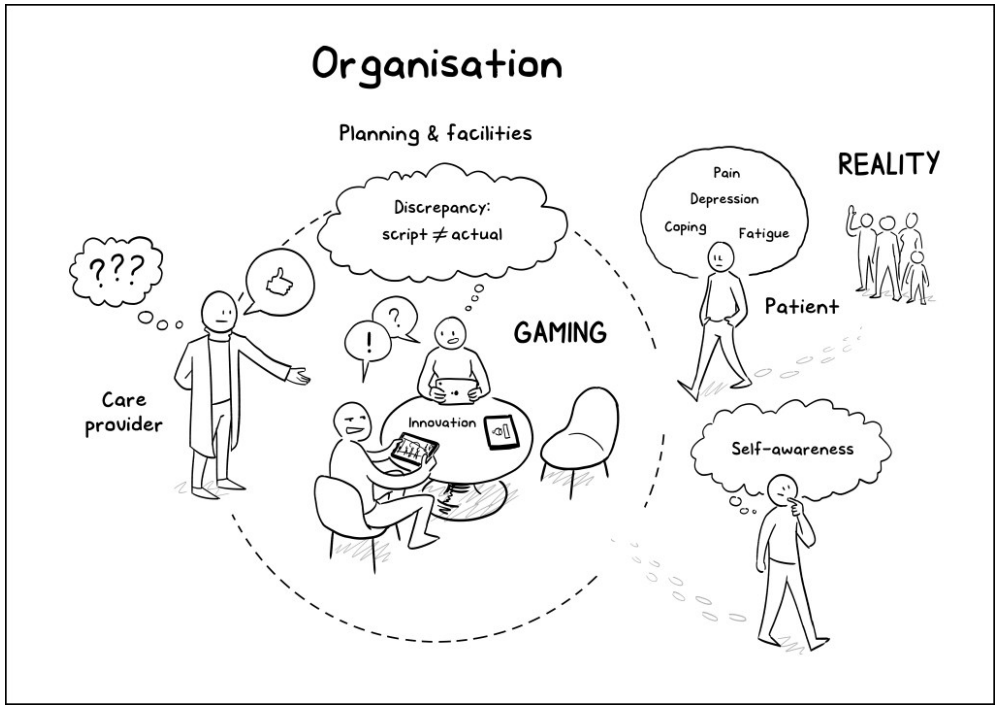
trained professionals and when more than half of the intervention group participants had (nearly) completed the experimental computer-based interventions. Furthermore, higher chances of clinically relevant symptom severity and functional interference outcomes were observed if experimental intervention descriptions mentioned exposure in vivo (a technique for adding neutral or positive associations between symptoms and conditional environmental stimuli). Plausible patient factors were also identified. Functional interference outcomes after computer-based intervention were higher in studies that included potentially depressed patients. At the same time, the results hinted at important different degrees of effect on somatic symptom outcomes between various functional somatic syndromes.

Finally, more statistically significant subgroup differences were found but these should be cautiously interpreted [90]. Therefore, only findings are highlighted that correspond to those of primary process evaluations [80, 359, 360]. For interpretation it is also important to know that these results suggest that cognitive behavioural approaches influence certain mechanisms (e.g., central sensitization), but it is not proven that they are effective against distinctive symptoms characterizing functional somatic syndromes [361].

7.2.3.2 Explaining serious gaming effects during multidisciplinary rehabilitation

By means of an experimentally embedded (mixed-methods) process evaluation (chapter 6), a model was constructed of how, why, and for whom serious gaming during multidisciplinary rehabilitation may be effective (see Figure 1). By triangulating results of semi-structured stakeholder interviews and mediation analysis, it was indicated that involvement in serious gaming can support complementary learning about mindfulness (i.e., self-awareness) and positive changes in depressive mood. For this it was crucial that patients felt “confronted with themselves” during serious gaming intervention. Therefore, mindfulness and self-discrepancy theory were chosen to describe (non-observable) mechanisms that may underlie learning from serious gaming. The discussion of chapter 6 elaborates upon this. Care provider-led ‘debriefings’, for sharing of various experiences after serious gaming and transferring these into individual learning, were perceived important for both acceptance and learning.

Figure 1: A programme theory of how serious gaming outcomes are produced in context



However, qualitative and quantitative findings also suggested that patients may not be triggered by a serious game like that, or for whom additional care provider guidance is particularly needed. Care providers expected that patients with difficulty to engage with serious gaming may be those that benefit the most. Patients expected no effect when focusing on pain control and experiencing no problems of emotional functioning. Based on that, stronger learning (mindfulness) and health outcome changes (depressed mood, pain intensity, and fatigue symptoms) were hypothesized and found for patients that less frequently use pain coping or active coping styles. Therefore, it is proposed that serious gaming may work best in those patients who (still) experience difficulty with reducing negative mood by approaching achievable goals, not truly pain-contingent, concerning favourable states of mind during or after social interactions.

The process evaluation also assisted in developing new theory about 'when' serious gaming will work. Qualitative findings suggested that serious game LAKA

may work due to the compatible (mindfulness) approach and relatively advantageous aspects of serious gaming within the larger treatment programme. Still, its complementary effect may have been sub-optimal due to limitations of the design (e.g., feedback provision). Qualitative and quantitative findings indicated better learning results (mindfulness changes) when planning of sessions for patients succeeded such that all 4 sessions were followed in quick succession (within 2 weeks maximally) and provided opportunity to interact in a group with other patients.

These early indications of contextual influences for serious gaming that are based on a particular application and health care context can be related to other work on games for health. Previous literature studies included highly diverse games for health, and sought to explain differences in effects by differences in game designs processes, features, comparators, follow-up terms, settings, users and targeted mechanisms of change [30, 43, 44, 356]. The findings of those studies raise the question of whether and how patient participation in the design of functional characteristics could have resulted in more favourable patient perceptions or outcomes [319]. It also counters the belief that the level of effectiveness found in this case of was limited compared to other serious games due to a relatively short duration of play. This suggestion is in line with a recent meta-analysis on serious games for health behavioural change that found no association between outcomes and duration of play (mean 3.8 hours, SD unreported) [30]. However, duration may generally be much shorter for serious games than for entertainment games. One could also suspect that our study only included adult patients whereas stronger effects may be found in children and adolescents; the more obvious target group [44, 356]. Finally, a trend seen both for computer-based intervention in the target group (chapter 2) and for serious games for changing behaviour, is that experimental components of larger programmes show weaker effects than stand-alone interventions [30].

7.3 METHODOLOGICAL CONSIDERATIONS

This thesis reports on an adequately scaled outcome evaluation, which was needed to answer the primary research question and complement the literature on the effects of serious gaming on health outcomes [43]. Tentative propositions, including a programme theory on serious gaming, integrate new explanatory

insights within existing literature. These are open to further support, refutation, refinement and expansion.

In line with medical research council guidelines, the research approach in this thesis developed towards an increasingly theoretical and contextual focus and more creative application of methods for evaluating complex interventions in real health care settings [24]. First, a pragmatic approach was taken to prepare for a full-scale outcome evaluation in particular local health care setting. Next, a realist approach was taken (see paragraph 6.3.1) in pursuit of producing more transferrable insights for future implementation in other, similar, and real health care contexts. However, the feasibility study already incorporated realistic tendencies with its focus on explaining usage by characteristics of patients and their planning processes. In other words, process analyses were used at all stages of empirical investigation to gain theoretical and contextual insight and inform practice. The set-up for outcome evaluation was also pragmatic as it was designed with acceptance of practical limitations to controlling intervention allocation, selection of (outcome) measures, patients (e.g., diagnostic classification and screening), care providers, and care organizations.

When considering the present methodological issues within the field of biopsychosocial intervention research, the empirical research approach of this thesis contributed more to progress for external than for internal validity. This may have suited the topic of interest well. External validity of the findings was strengthened by studying natural variation within a sample of patients from a regular health care context that did not self-select for computer-based intervention and were not informed in a way that could raise expectations about (missing) complementary effects of serious gaming. However, this also opened the door for internal validity threats, including unobserved dissimilarities between study groups, lack of indisputability that findings apply for particular classes of patient conditions, and sub-optimal measurement of mechanism and outcome indicators. Specifically, the use of additional or alternative measures of biopsychosocial mechanisms, outcomes (e.g., cognitive performance tests or physiological measures of stress), or costs were desired.

When looking back at the research from a realistic perspective, which was not adopted explicitly from the start, one could suspect that more explanatory focus and collaboration with local stakeholders at early stages could have benefitted ongoing development of programme theory as well as the serious

gaming intervention. For example, self-discrepancy theory could have been used earlier for interpretation and measurement selection. It was considered, however, that fixating on leads from unsaturated qualitative data on this topic during the pilot stage would limit openness to other ways to conceptualize mechanisms. Specifically, information about experienced self-discrepancies already came up during the pilot phase when interviews were held with a focus on collecting saturated data with regard to explanations for acceptance and usage. However, as we did not yet intended to collect saturated data on the topic of learning mechanisms, it was not clear at this point that such experiences would be as common and consistent (necessary) experience for learning as they turned out to be later; during the final process evaluation stage. A more consistently realistic approach might have led us to extend empirical variation in care provider and organizational contexts for more interesting insights. However, it could be questioned if seeking more variation at higher levels of context would be sensible when impeding statistical power (or challenging the sampling procedures) while the quasi-experiment could usefully support explanatory purposes by indicating *that* presumed causal effects operate (i.e., attribute outcome variation blind of what these effects essentially are [362]). This illustrates that taking a realistic approach encourages skill and courage to think mechanisms through thoroughly and open-mindedly, and to decide smartly on research focus and resource allocation.

Pragmatic and realistic principles legitimized the use of mixed-methods designs in two stages of empirical research [347]. Both agree that qualitative and quantitative methods are not epistemologically incompatible but can compensate for each other's weaknesses in addressing certain research questions. The discussions of the feasibility study, study protocol, and process evaluation chapters (3, 4, and 6) deal with several strengths and limitations of how mixed-methods were planned and executed. To this, it should only be added that involvement of experts that were unfamiliar to the local setting (as mentioned in the protocol) remained limited until the end of thesis.

Systematic review methods followed the Cochrane-guidelines, which was a decision taken at the start of the trajectory. Accordingly, methods of literature reviewing can be considered to be systematic, comprehensive (for the published peer-reviewed literature), and rigorous. Importantly, the use of the Cochrane tools showed that recurring general limitations of experimental studies of

biopsychosocial interventions also apply to research into computer-based intervention. Moreover, trial reports provided limited in-depth explanatory information on relationships between outcome patterns, mechanisms, patient characteristics, and other circumstances of computer-based intervention. To complement such limitations, different guidelines exist for a realist approach to synthesizing existing evidence [363]. They are not 'inferior' review methods, but are suitable to different, more explanatory, research goals [364]. Use of realist synthesis procedures may likely have resulted in the use of stakeholder participation for focusing the research, incorporating relevant sources of any type (i.e., not only controlled experiments), and performing iterations of search and analysis [365, 366].

7.4 SUGGESTIONS FOR FUTURE RESEARCH

It is encouraged to replicate, refute, extend, and refine the explanatory findings from this dissertation, such as the programme theory for serious gaming (see Figure 1). This implies, amongst other things, integrating research on clinical outcomes and implementation for a public interest [367]. Replication and refutation efforts could aim at complementing methodological limitations of this dissertation. Programme theory development could focus on a broader range of outcomes, including cost-effectiveness and reach (scale-up to patients and settings). In the future, realist (economic) approaches may provide useful deeper insights for balancing costs and benefits of interventions for triggering biopsychosocial mechanisms in different patients and contexts [368]. These may inform on how to use scarce resources more efficiently and keep treatments financially viable for patients whom are most likely benefit at certain times and places [9, 26, 27].

Programme theory development could also address a potentially endless variety of computer- or game-based interventions, patients, care providers, and wider organizational contexts (e.g., on financing and legislation). For example, patients could be more strongly involved in researching features of serious gaming that could be re-designed with emphasis on how learning, through self-discrepancies, can be maximized while minimizing disengagement. It could be studied how understandings about predictive patient coping behaviours for effectiveness could be used in allocation or tailoring for better outcomes. More studies could focus on dynamics of professional guidance and therapeutic

alliances, and their importance for engagement in computer-based intervention and mechanisms of patient health improvement [369]. Surely, the presented literature review suggested that computer-based interventions with care provider support, especially those that also included telephone calls, have higher completion rates. Understandings of organisational implementation processes for recipient use of computer-based intervention could be extended by complementing technology acceptance models with theory on normalization processes [370] and decisional framing (e.g., the ethically sensitive strategy of nudging as a 'default option') [371]. This thesis showed that improvements of local implementation processes (see chapter 4), which involved local implementers and focused at incorporating serious gaming as a 'normal' treatment component, accounted for a large increase in the proportion of study participants that completed the serious game LAKA. This happened without corresponding changes in acceptance perceptions. For allowing contributions of research to practical effort (i.e., scale-up), important stakeholders could be involved in all stages of evaluation, starting when choosing amongst many possible directions.

More use of realist approaches is also suggested to inspire debate on research foci and selection of methods for studying complex biopsychosocial interventions more generally. RCTs may not be the single best choice for advancing the field. Realists have been criticizing the status of the RCT as the golden standard for every question, stage, and circumstance for evaluation [362]. A point taken from the realist perspective is that high quality RCTs can establish 'attribution' but cannot discover 'generative' causation or underlying (non-observable) mechanisms. Thus, RCTs do not yield new transferable insights on how and why an intervention package works, for whom and when [372]. Meanwhile, important stakeholders make a valid point when stressing the need to conduct better RCTs for determining the effectiveness of biopsychosocial approaches: more detailed reporting in accordance with prospective registration, smarter handling of obstacles to double blinding against bias induced by placebo and nocebo effects, more consistent case-classification and identification, and improved outcome measures covering multiple biopsychosocial levels [373].

Currently, the number of RCTs on health outcome attribution to computer-based interventions has been continuing to grow despite they might not add much new information, do not deal with recurrent risks of bias that raise

concern about the evidence for biopsychosocial management strategies, and are not equipped for gathering needed theoretical and contextual insight. Numerous RCTs were published after the final date of our systematic searches, and their methods and results generally appear to be similar to past studies with passive comparisons [374-386], as well as for those with active comparisons [357, 358, 379, 385, 387, 388]. Therefore, it is suggested that future RCTs on biopsychosocial interventions focus more on general theoretical underpinnings and improvement of methods. Moreover, better understandings of relationships between context (including delivery modes) and mechanisms require complementary qualitative and mixed methods studies performed in regular health care contexts. Gathering best possible information on outcome change attribution should less often be seen as primary and necessary and more often as supportive and desirable for informing improvement in practice. The need, usefulness, and success rate of a RCT may grow with understandings of ideal circumstances for influencing specific mechanisms.

7.5 IMPLICATIONS AND RECOMMENDATIONS

The findings of this thesis imply that (1) computer- and game-based interventions can be effective in patient learning about dealing with chronic somatic symptoms and reducing burden on physical and emotional functioning, and that (2) contexts of implementation can be understood and managed for increasing chances that patients engage and achieve clinically important benefit. However, patients, care providers, and policy makers should not expect that provision of these technologies will generally result in good adherence and important health benefit in all respects, for all target patients, and in any circumstance. Being sensitive to the right circumstances for a patient that provides opportunity to benefit requires more insight. This kind of insight is illustrated with these anecdotes for serious gaming during multidisciplinary rehabilitation:

A patient recognizes that serious gaming complements 'theoretical sessions' by providing opportunity to safely experiment with alternative behavioural goals in a simulated environment with salient behavioural opportunities and emotional consequences.

A patient who is aware of problems in concentrating on activities sees serious gaming as a pleasant diversion from other efforts in rehabilitation, and concentrating is perceived to be eased and promoted during gaming.

For future development it is important to know that a computer or game-based intervention may support any cognitive behavioural approach equally effectively, but the approach should be valid and its strategy relatively advantageous within an intended context. Effectiveness of computer-based intervention can probably be strengthened by including guidance in exposure in vivo. For increasing chances of adoption, it matters if computer and game-based intervention designs motivate the recipients: triggers perceptions of being useful, trustworthy, easy to use, and enjoyable. Furthermore, it is plausible that immersive technologies, like simulation features of serious games, trigger more attentive use and strengthen effects. However, time and budget are to be weighed against preventing perceived limitations in design and adjustment to idiosyncratic preferences (flexibility and personalization).

Professional care provider support, which could take the form of telephone contact in case of internet-delivery and timely face-to-face debriefing in response to experiences in case of serious gaming during clinical treatment, is a highly plausible facilitator of programme engagement. Herein, care providers should anticipate patients who are generally less inclined to actively deal with obstacles such as gaining access to software with security measures (e.g., logging in) or who anxiously hesitate, perceive less ease or control, and make less use of application content (in available time). It is worth the effort to keep them engaged in the learning objective. Effectiveness could be strongest if the learning objective and health outcome are (still) noticeably improvable and important to a patient. This could be considered in allocation and tailoring decisions, maybe with help of screening tools for psychological distress and active or 'problem-focused' coping and pain coping.

A health care organisation that expects patients to adhere to a computer- or game-based intervention should carefully consider implementation processes for facilitating access, also because one cannot rely on patient motivation and planning only to do so. Importantly, larger shares of intended populations may adhere when facilitating conditions of usage that fit patients' routines of treatment (i.e., enable usage in clinics, interaction with care providers and peers,

and planning in connection to other therapy sessions) and of technology usage at home (i.e., use of various computer platforms). Finally, good planning and facilitation of serious gaming could also be of direct importance for effectiveness. A lack of coordination as such could restrict access to serious gaming for those patients who, under better circumstances, show most potential to benefit.

Main recommendations (for the future) are formulated to various actors:

Patients

- When considering computer-based intervention: select a computer or game-based intervention that includes guidance by expert care providers, or be strongly prepared to engage independently in exercising and applying new perspectives and behaviours under challenging circumstances.
- Check if the features of the programme can be used on a computer platform and with (a) communication channel(s) that one routinely uses.
- Choose a programme that is aimed at improving something about health that can still be improved and is important to you.
- A moderate amount of computer gaming can be healthy. Games can be used for relieving stress and being challenged to solve problems. However, one cannot expect that games generally have sustainable positive effects on quality of real life. Serious games can be valid health services that provide modest chances for health benefit.

Care providers

- Consider relative advantages functions that computer- and game-based interventions might have in local circumstances, for example: to 'outsource' efficacious but highly routine patient instructions, to encourage the independent involvement of individual patients, or to create room during scarce direct contact hours for matters that mostly demand your personal approach and professional expertise.
- If using serious gaming interventions, focus on facilitating and supporting usage by patients who show emotional distress and consider themselves not in control of how they live with pain and stress. Because these patients may have the best chances of achieving clinically important benefit. Maybe one does not

want to restrict access for serious gaming for other patients, as they could also enjoy it and share experiences for the benefit of other patients.

Health care organisations

- The serious game LAKA used in this study aimed to offer acquaintance with forms of skill training and encouragement for repeating those skill trainings in the context of daily life. In line with this function, serious gaming can be used within protocols to make it easier for patients (supposedly novices) to plan for skill use and prolonged exercise (e.g., many hours of meditation), which can ultimately have structural (neurologic) effects [42].
- Only implement computer- or game-based elements with clear and valid rationales that are compatible to existing treatments and organisational values and norms, and relatively advantageous to other delivery modes in the treatment process. It is advisable to be cautious about adding computer or game-based features on top of existing processes, and to consider incorporation as part of redesigning (chains of) biopsychosocial programs at large.
- Integrate usage carefully in the routines of patients and care providers, including the technologies they already use.
- Plan and facilitate such that patients do not lose interest. This is done by enabling patients to complete serious gaming within a short period of time, to receive debriefing by a care-provider immediately after game-play, and to share and compare experiences with other patients.
- Make sure that usage continues to be flawlessly technically facilitated (take care of patients with special needs, ensure availability of technical assistance, ensure that software is maintained, etc.).

Developers (e.g., companies)

- (Continue to) develop mindfulness-based serious gaming, starting with improvement at the 'intervention level' of implementation. Simply stated: improve the application (software code) with a focus on successful specifications and changing those that may be unfit to future intended contexts. There are potential improvement areas, certainly for better user experiences (acceptance) and maybe also for patient learning, which relate to

increasing adjustment to individual preferences and the specificity and clarity of automatically generated performance feedback.

Network of stakeholders

- Build a collaborative network of stakeholders from public- and private organisations, including patient and care provider representatives, health care organisations, health insurers, authorities, companies, knowledge institutes, with the purpose of organising conditions for scaling-up and sustaining a serious gaming intervention for supporting patients in developing coping ability for reducing burdens of chronic somatic symptoms. A business case for such a serious gaming approach may be built on its large potential reach, because modest individual health benefits and substantial initial investments should be expected. A network form of governance may be necessary for gaining required knowledge and to act upon organizational/institutional level implementation barriers and facilitators (e.g. various actor visions, goals, and financial motives). Researchers may have a role in such a network by facilitating partners continuously in informing programme demands.

7.6 FINAL NOTE

Readers of this thesis may confront some paradoxes. First, this thesis primarily questioned about the effectiveness of serious gaming, while a computer application may better be seen as a set of features, introduced within a health care context, which cannot produce an effect by itself. Is that not like asking about the effectiveness of the container and colour of a pill? Secondly, the response of environments to health conditions characterized by persistent, often unexplained, pain and fatigue can threaten the identity of patients [389]. Is it not provocative to suggest that something 'unserious' like a computer game could become some part of 'a solution'? Third, although the motive to use computers is often to save time and costs, only a very small effect is achieved after considerable investments. Is developing and researching serious games really worth the effort?

This study suggests that there is potential in computers and games for use as complementary triggers of mechanisms that actually lead to important health improvements. Therefore, serious games might become to be known in the future as the 'best' delivery mode for certain functions/mechanisms of health improvement for certain patients in certain conditions. Finding and arranging such

circumstances, for example in chronic pain management, may only be slowed down by pursuit of judgement about: if games are good or bad for health, if health conditions reside in the body or is in the mind, or if serious games (research) are cost-effective at this point in time. This is far from arguing blind trust. Maybe, for the time being, focusing rigorously on questions of 'how', 'why', 'for whom', and 'when', is more productive and directive for taking serious games seriously. Hopefully, its potential can be realized steadily despite that it will undoubtedly also go slowly. Maybe, the challenge is to be forbearing, persevering, enthusiastic, non-judgemental, and aware and attentive to the questions of now.

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9 UITGEBREIDE NEDERLANDSE SAMENVATTING

Deze samenvatting geeft een vrij volledig beeld van de inhoud van het proefschrift. De inhoud hiervan is in de hoofdstukken van een bronvermelding voorzien. De lopende tekst gaat over de aanleiding voor het proefschrift, de algemene probleem- en vraagstellingen, de aanpak van het onderzoek (kort) en conclusies van de verschillende hoofdstukken. De laatste twee paragrafen beschrijven de antwoorden op de onderzoeksvragen en aanbevelingen voor onderzoek en praktijk. Meer gedetailleerde informatie over achtergronden, theorie, onderzoeksmethoden en statistiek is in tekstvakken beschreven.

9.1 AANLEIDING VOOR HET PROEFSCHRIFT

In de periode 2011-2013 werd door een Nederlands revalidatiecentrum het computerspel 'LAKA' ontwikkeld. Het spel diende als aanvullend leermiddel tijdens een multidisciplinair revalidatieprogramma voor patiënten met ‘complexe’ chronische pijn, vermoeidheid of houding- en bewegingsapparaat klachten.
Het spel LAKA bood 1) een virtuele omgeving om te oefenen met besluitvorming in onvoorspelbare sociale interactiescenario’s en 2) instructies en aanmoediging om te oefenen in vaardigheden van gerichte aandacht en open bewustzijn (zie tekstvak 1). Deze vaardigheden kunnen positief bijdragen aan het ondervinden van minder hinder van symptomen en emotionele lasten en meer psychisch welzijn, deelname aan sociale rollen en kwaliteit van leven. Mogelijk kan een computerspel bijdragen aan het inspelen op variërende of veranderende voorkeuren van patiënten. Wellicht is de ervaringsgerichte manier van leren die de virtuele omgeving van games mogelijk maakt bijzonder nuttig voor een deel van de patiëntenpopulatie.

Tekstvak 1: Beschrijving van de computergame ‘LAKA’

LAKA is een avonturenspel dat eenvoudig met computermuis of touch screen te besturen is. Een speler kiest een persoonlijke Avatar (man/vrouw) die hem/haar vertegenwoordigt op een wereldreis. Het verhaal wordt geïntroduceerd waarin Avatar weergegeven wordt als iemand met een terugslag in de lichamelijke en sociaal-emotionele staat en vastberaden is om zijn/haar leven te veranderen. De Avatar ontmoet de virtuele leermeester genaamd Laka, die de Avatar uitdaagt om bewuste keuzes te maken in ontmoetingen met andere mensen tijdens de reis naar 4 bestemmingen: Londen, Turkije, Azië en Afrika. Op elk van deze bestemmingen treft de Avatar 4 verschillende scenario’s waarin hij/zij lastige keuzes moet maken waarbij reacties van de omgeving kunnen variëren en moeilijk te voorspellen zijn, bijvoorbeeld door onbekende lokale gebruiken en wispelturige karakters. Op elk moment zijn er 5 keuzemogelijkheden die in uiteenlopende mate blijk kunnen geven van ‘generositeit’, ‘morele discipline’, ‘verdraagzaamheid’ of ‘enthousiast doorzettingsvermogen’ (bijvoorbeeld een ander helpen of vasthouden aan gesteld doel). Tussen deze ontmoetingen is er gelegenheid tot afleiding in de vorm van een puzzel of besturen van een voertuig (minigames) om op de volgende locatie te komen. Aan het einde van elke bestemming volgt een ontmoeting met Laka. Die vraagt een beoordeling te geven van hoe het is gegaan, deelt zijn eigen visie daarop en toont in hoeverre de Avatar en Laka het eens waren over de gemaakte keuzes. Tijdens de reis naar een volgende locatie wordt er instructie gegeven voor het uitvoeren van oefeningen, van 3 minuten lang, die gericht zijn op het verbeteren van gerichte aandacht en open bewustzijn. Na vier bestemmingen volgt een feestelijke afsluiting en de uitnodiging om de reis opnieuw, maar anders, te beleven.

Of het daadwerkelijk haalbaar en effectief is om een computergame met dit doel in te zetten, hoe dat werkt en waarom, voor welke patiënten en onder welke omstandigheden was niet bekend. De ontwikkeling van LAKA bood gelegenheid om hier meer over te weten te komen.

9.2 INLEIDING

9.2.1 Het gezondheidsprobleem; aard en consequenties

Iemand met 'chronische pijn' heeft langer dan 3 of 6 maanden last van pijnklachten: langer dan herstel van schade aan organisch weefsel gewoonlijk duurt. Vaak kan een specifieke medische oorzaak van pijn, zoals aandoeningen van migraine of artrose, na gebruikelijke medische onderzoeken vastgesteld worden. In veel andere gevallen wordt geen bestaande ziekte gediagnosticeerd die afdoende verklaring biedt voor de symptomen, zoals bij patiënten met fibromyalgie, chronische lage rugpijn, of spanningshoofdpijn. Functionele belemmeringen bij lichamelijke klachten die niet goed verklaard kunnen worden na gebruikelijk medisch onderzoek worden veelal geclassificeerd als "functioneel somatische syndromen". Functioneel somatische syndromen kunnen naast pijn ook gekenmerkt worden door andersoortige langer dan 6 maanden aanhoudende symptomen, zoals vermoeidheid, hartkloppingen, duizeligheid, of oorsuizen. Verschillende soorten (onbegrepen) lichamelijke klachten gaan vaak met elkaar en met psychische klachten samen, vooral depressie en angst. Andersom kunnen pijn en vermoeidheid ook symptomen van een depressie zijn. Wanneer lichamelijke klachten gepaard gaan met psychische lijden, zijn de functionele beperkingen van patiënten over het algemeen ernstiger. Dit hindert vervulling van belangrijke sociale rollen, zoals studie, werk en het gezinsleven. Chronische pijn-condities zijn 'complex' naarmate persoonlijke en omgevingsomstandigheden invloed hebben op het algehele functioneren. Deze gezondheidscondities zijn een ernstig probleem voor individuen die eronder lijden en, vanwege de hoge prevalentie en kosten, ook voor maatschappijen als geheel (zie tekstvak 2).

Tekstvak 2: De prevalentie en kosten van chronische pijn

Onderzoek uit 2005 schatte dat 1 op de 5 Europeanen chronische pijn heeft. Niet iedereen heeft daar evenveel hinder van. Afhankelijk van definities van pijn, functionele belemmering, en demografische kenmerken variëren schattingen van wereldwijde prevalentie van chronische pijn tussen de 7% en 64%. Op basis van een grote wereldwijde epidemiologische studie werd gesteld dat chronische lage rugpijn gedurende het leven van mensen wellicht hogere lasten met zich meebrengt dan elke andere ziekte. In Amerikaans onderzoek werden zorgkosten van chronische lage rugpijn patiënten 2 maal hoger geschat dan voor mensen zonder deze aandoening. Indirecte kosten door verzuim en verlies van arbeidsproductiviteit werden nog iets hoger geschat dan de directe medische kosten.

9.2.2 Biopsychosociale oplossingen en hoe goed deze werken

Omgaan met chronische pijn en functioneel somatische syndromen is een grote uitdaging voor patiënten, zorgverleners en het zorgsysteem. Aanbod van zorg is veelal gebaseerd op het biopsychosociale model (tekstvak 3).

Tekstvak 3: Biopsychosociale en psychotherapeutische benaderingen

Volgens het biopsychosociale model zijn biologische mechanismen van pijn (bijvoorbeeld nociceptie) sterk verbonden met psychosociale mechanismen (cognities en gedrag in reactie op pijn). Een bekende biopsychosociale verklaring is dat centrale zenuwstelsel bijzonder gevoelig reageert op prikkels van binnen en buiten het lichaam. Opkomende pijnsignalen in het zenuwstelsel worden niet goed gedempt door neergaande signalen naarmate iemand pijnervaringen vreest, vermijdt (niet 'accepteert'), of catastroferende gedachten heeft. Daarop suggereerden studies dat psychische behandelingen gericht op verandering van cognities gunstige effecten kunnen hebben op lichamelijke symptomen en (emotioneel) functioneren (zie tekst vak 2). Op zulk soort veranderingen richten ook multidisciplinaire revalidatieprogramma's richten zich met, onder andere, psychologische behandelingen, fysieke activering en werkgerichte interventies.

In psychotherapeutische benaderingen, zelfstandig of als onderdeel van revalidatie, maakt men onderscheid tussen een '2e golf'; gekenmerkt door nadruk op aanpassing van specifieke cognities, en een zogenaamde 3e golf; vooral gericht op respons vaardigheden binnen een functionele context, zoals bewust en gecommitteerd zijn aan doelgerichte actie. Wat in essentie de verschillen zijn in werking en resultaten van deze benaderingen zijn nog onderwerp van onderzoek. De aanpak en leerdoelen van het spel LAKA zijn tijdens het onderzoek geïnterpreteerd als passend bij een '3e golf' benadering.

Hierbij is het de bedoeling dat behandeling stapsgewijs geïndiceerd wordt, in volgorde van oplopende intensiteit: erkenning en conservatief voorschrijven van medicatie door een (huis)arts, psycho- of fysiotherapeutische behandeling,

specialistische behandeling in de 2e lijn en multidisciplinaire revalidatie (geïntegreerde medische, psychologische, fysieke en werkgerichte interventies). Veel contacten met verschillende zorgverleners levert voor patiënten veelal geen duidelijkheid op, maar wel risico op schade.

Een beperking voor besluitvorming over het vormgeven en aanbieden van interventies die op biopsychosociale uitgangspunten gebaseerd zijn, is overtuigdheid van het bewijs over of, hoe, waarom, voor welke patiënten en onder welke voorwaarden gewenste uitkomsten ontstaan. Onderzoeken naar effecten van biopsychosociale programma's op lichamelijke symptomen en functionele belemmering voor patiënten tonen over het algemeen bescheiden effecten. Zo bescheiden dat een groot deel van de patiënten die de behandeling ontvangen niets of nauwelijks iets van verbetering merkt. Dit suggereert dat deze vormen van zorg aan veel patiënten geen hoge, maar vooralsnog wel de beste, kansen bieden voor verbetering in hun dagelijkse functioneren. Ook is er kritiek op de kwaliteit van de studies naar effectiviteit van biopsychosociale zorg. Dit laat ruimte voor zowel twijfel als verbetering (zie tekstvak 4). Onzekerheid blijft bestaan bij het ontbreken van sluitende verklaringen in biologische oorzaken voor lichamelijke symptomen en disfunctioneren: dat zegt immers niet dat zo'n specifieke medische oorzaak er niet is en dat psychosociale aanpassing bijzonder profijt op zal leveren.

Tekstvak 4: bekritiseerde aspecten van kwaliteit van doelmatigheidsonderzoek

Risico op beïnvloeding van onderzoeksresultaten door vooringenomenheid kan beperkt worden uitgesloten doordat in experimenten met biopsychosociale interventies:

- Niet altijd gebruik maakten van eenduidige diagnostische criteria bij de selectie van patiënten die aan onderzoeken deelnamen. Ook is het mogelijk dat er 'zelfselectie' plaatsvindt waarbij bepaalde patiënten met een lagere of hogere kans op te profiteren van interventies niet aan onderzoeken meedoen, of tijdens het onderzoek uitvallen.
- Alleen gebruik maakten van zelf gerapporteerde uitkomsten (vragenlijsten) terwijl maatregelen om deelnemers onwetend te laten over de aard van interventie die ze ontvangen in de praktijk onpraktisch zijn. Daardoor is het mogelijk dat resultaten beïnvloedt zijn door positieve verwachtingen van patiënten over de experimentele behandeling geloven, of negatieve verwachtingen van patiënten die ter controle op een wachtlijst werden geplaatst.

Vanuit wetenschappelijk perspectief is er daarom behoefte aan studies die ook gebruik maken van bijvoorbeeld biologische indicatoren.

9.2.3 Onderzoeksvragen en beloften m.b.t. computer- en gaming- gebaseerde interventies

Mogelijk kunnen patiënten ook profiteren van verbeteringen in de wijze waarop bestaande biopsychosociale interventies aan patiënten worden aangeboden. Interesse gaat uit naar digitale technologieën, zoals het internet, mobiele apps, serious games en virtual reality voor verbeteringen in de toegankelijkheid, beleving of motivatie, personalisatie, of kosteneffectiviteit van het zorgaanbod. Studies laten veelbelovende resultaten zien met 'serious games', ofwel computergames die zowel voor het plezier als een gezondheidsdoel ontworpen worden. Met dit middel kan men ook bescheiden verbeteringen bereiken in kennis, cognities, gedrag en psychische symptomen. Om hier meer zekerheid over te krijgen was er nog behoefte aan meer, groter opgezette, studies.

De eerste onderzoeksvraag: *In welke mate (in welk opzicht en voor hoe lang) zijn computer-gebaseerde gedrag veranderende interventies effectief voor patiënten met complexe chronische somatische symptomen?*

Deze vraag omvat: In welke mate (en in welk opzicht) is multidisciplinaire revalidatie met serious gaming effectief in vergelijking met multidisciplinaire revalidatie zonder serious gaming?

Een hindernis om deze vraag goed te kunnen beantwoorden is dat veel patiënten die deelnamen aan eerdere experimenten met computer gebaseerde programma's vroegtijdig stopten met het gebruik ervan. Dit riep de vraag op of inzet van serious gaming voor gebruik door patiënten tijdens een multidisciplinaire revalidatiebehandeling op substantiële schaal wel haalbaar is. De vraag is ook welke patiënten het accepteren, om welke redenen en onder welke voorwaarden.

De tweede onderzoeksvraag: *Waarom en voor wie is serious gaming haalbaar, d.w.z. geaccepteerd, gebruikt en implementeerbaar als een aanvullende interventie tijdens multidisciplinaire revalidatie van patiënten met complexe chronische somatische symptomen?*

Ook is meer zorgvuldig onderzoek essentieel om te begrijpen wat voor technologieën op de meest effectieve manier interventies ondersteunen, hoe dat in zijn werk gaat, voor welke patiënten, onder welke omstandigheden en waarom dat zo is. Mogelijk kan hierover meer inzicht verkregen worden met behulp van een realistische evaluatie benadering (tekstvak 5): inzichten voor beter geïnformeerde beslissingen over computer- en gaming interventies door betrokken patiënten, zorgverleners, aanbieders, ontwikkelaars/bedrijven en beleidsmakers. Dit leidde tot de derde en laatste onderzoeksvraag.

Tekstvak 5: Realistische onderzoek benadering

Een realistische onderzoek benadering is mogelijk bijzonder nuttig om meer theoretische en contextuele inzichten te krijgen over de werking van programma's, interventies, of beleid in complexe sociale omstandigheden. Tegen eenzijdige gerichtheid op het betrouwbaar vaststellen van gemiddelde effect op leren en gezondheidsuitkomsten, kenmerkt zo'n benadering zich in gerichtheid op ontwikkeling van 'programmatheorie': duiding van hoe en waarom productieve redenaties van interventiegebruikers geactiveerd worden onder bepaalde omstandigheden van het dagelijkse leven (bijvoorbeeld historische of sociale omgevingskenmerken) of wijze waarop programma's/interventies daadwerkelijk worden ontvangen. Dergelijke inzichten kunnen beslissingen over ontwerp, selectie, toewijzing, afstemming (personalisatie of advies en feedback) en implementatie van nieuwe interventies waarschijnlijk beter informeren.

De derde onderzoeksvraag: *Hoe, waarom, voor wie en wanneer zijn computer-gebaseerde gedrag veranderende interventies effectief bij patiënten met complexe chronische somatische symptomen?*

Dit bevat: Hoe, waarom, voor wie en wanneer is multidisciplinaire revalidatie met extra serious gaming effectief in vergelijking met multidisciplinaire revalidatie zonder serious gaming?

9.3 FUNCTIE, OPZET EN RESULTATEN VAN DE UITGEVOERDE ONDERZOEKEN

In het onderzoek zijn stappen doorlopen in (a) interventietheorie ontwikkeling, (b) pilot/haalbaarheidsonderzoek, (c) uitkomsten en procesevaluaties en (d) implementeren. Dit leverde 5 gerapporteerde onderzoeken op die in het vervolg 1 voor 1 besproken worden.

9.3.1 Systematische literatuurstudie en meta-analyse

Hoofdstuk 2 biedt sterke informatie voor het beantwoorden van de **eerste onderzoeksvraag** en indicaties met betrekking tot **onderzoeksvraag 3**. Dit hoofdstuk vervult ook de functie om bevindingen over de effectiviteit van serious gaming binnen een kader van bestaande evidentie te plaatsen over de effecten van diverse computerinterventies voor patiënten die goed vergelijkbaar zijn met patiënten die een multidisciplinaire revalidatieprogramma volgen.

Tekstvak 6: systematische review en meta-analysemethoden

Kwaliteit van de literatuurstudie

Minstens 2 onderzoekers beoordeelden onafhankelijk (1) of studies aan de gestelde in- en exclusiecriteria voldeden, (2) of risico's op resultaat beïnvloeding door vooringenomenheid hoog, laag of onduidelijk waren en (3) welke benaderingen, technieken en aanvullende aanbiedingswijzen voor gedragsverandering deel uitmaakten van de interventies. Daarnaast werd informatie uit de artikelen gehaald over diverse kenmerken van deelnemende patiënten (aantallen of gemiddelden in o.a. geslacht, leeftijd en opleidingsniveau), methoden (zoals toegepaste vergelijkingsgroepen) en uitkomsten: gemiddelden en standaarddeviaties van de experimentele groepen in lichamelijke symptomen, kwaliteit van leven, functionele belemmeringen, cognities en depressie: direct en minstens 6 maanden na afloop van de interventies gemeten. Door middel van meta-analyses werd een schatting gemaakt van de grootte en heterogeniteit van gemiddelde verschillen in uitkomsten tussen experimentele en controlegroepen per uitkomstendomein en moment van beoordeling. Hierbij werden gestandaardiseerde gemiddelde verschillen uitgedrukt in proportie van een standaarddeviatie, waarbij >0,2 klein, >0,5 middelgroot en >0,8 groot is. Als schattingen substantieel varieerden tussen studies (I^2>0,4), dan werd verder verkend welke kenmerken van interventies, patiënten, of methoden met de uitkomstenverschillen samengaan.

Kwaliteit van de onderzochte studies

De combinatie van zelfrapportage door patiënten terwijl zij konden weten tot welke onderzoeksgroep zij behoorden was in vrijwel alle studies een bron van risico op resultaatbeïnvloeding door vooringenomenheid. Andere veelvoorkomende risico's waren uitval van deelnemende patiënten en het ontbreken van vooraf geregistreerde onderzoeksprotocollen. In meta-analyses werden geen statistisch significante resultaatverschillen gevonden tussen studies met een laag versus hoog of onbekend beoordeelde risicobronnen.

De gebruikte **methoden** bestonden uit het identificeren en analyseren van informatie uit gepubliceerde artikelen uit diverse wetenschappelijke databases over gecontroleerde experimenten waarin voornamelijk de computer gebruikt werd om ondersteuning te bieden bij gedragsverandering aan patiënten met chronische pijn of een functioneel somatisch syndroom. Meta-analyses werden

uitgevoerd om uitkomsten te relateren aan kenmerken die artikelen rapporteerden over interventies, deelnemende patiënten en onderzoeksmethoden (zie tekstvak 6).

Dit **resulteerde** in zoveel geïdentificeerde studies dat er meta-analyses uitgevoerd konden worden over maximaal 30 van de 46 onderzoeken en 3.387 deelnemers. De meeste studies onderzochten cognitieve gedragstherapieën via internet met gebruikelijke elementen zoals vaardigheidsoefening in ontspanning of meditatie, doelen stellen, herstructurering van cognities en ontwikkelen van persoonlijke waarden. De patiënt gerapporteerde uitkomsten waren voor interventiegroepen hoger, met een klein statistisch significant verschil, dan voor 'passieve' controlegroepen, zoals wachtlijstcondities, gebruikelijke zorg, patiënten informatie, of toegang tot online fora als een 'placebo' behandeling. Ook na minstens 6 maanden was er een statistisch significant klein positief verschil in gemiddelde uitkomsten te zien. Dit was niet het geval als er actieve controlegroepen werden gebruikt, zoals computerinterventies met minder uitgebreide of vooruitstrevende eigenschappen, face-to-face groepstherapie, of multidisciplinaire programma's zonder aanvullende computerinterventie. Variatie in effectschattingen tussen studies was voor cognities en depressie niet substantieel, maar voor de andere uitkomsten wel. Studies waarin interventies gekenmerkt werden door de begeleiding (via telefoon of e-mail) door getrainde zorgprofessionals en aanzetten tot blootstelling aan activiteiten (om nieuwe associaties te vormen) rapporteerden betere resultaten. Dat gold ook voor studies waarin deelnemende patiënten gemiddeld beter geschoold en jonger waren en bij aanvang last hadden van depressieve stemming.

Geconcludeerd werd dat er een minderheid aan bewijs van behoorlijke kwaliteit bestaat voor kleine, positieve en wisselende gemiddelde effecten van computer gebaseerde (cognitieve) gedragsverandering interventies, vergelijkbaar met traditionele manieren van aanbieden. Deze effecten kunnen ook duurzaam zijn. Daarmee blijven effecten grotendeels onvoorspelbaar en zullen veel patiënten de positieve effecten niet of nauwelijks opmerken. Er zijn diverse nader te onderzoeken aanwijzingen gevonden over kenmerken van interventies en patiënten waarbij effecten op diverse relevante uitkomstendomeinen beter of consistenter zijn.

9.3.2 Haalbaarheidsonderzoek

Hoofdstuk 3 onderzocht **onderzoeksvraag 2** en diende ook om te informatie te bieden voor latere evaluatieprocedures met meer succes in het werven en behouden van deelnemers tijdens een groter opgezette evaluatie van LAKA. Het doel was om uitleg te kunnen bieden over diverse aspecten van haalbaarheid bij inzet van LAKA tijdens multidisciplinaire revalidatie, waaronder relaties tussen variatie in mate van acceptatie en gebruik en verschillen in percepties en kenmerken van patiënten.

Een pragmatische benadering van gemengde kwantitatieve en kwalitatieve **methoden** werd toegepast. Tijdens een gelimiteerde onderzoeksperiode van 4 maanden werd LAKA toegankelijk gemaakt voor patiënten die voor complexe chronische pijn, vermoeidheid, of houding- en bewegingsapparaat klachten een 16 weken durend multidisciplinair revalidatieprogramma volgden binnen 4 locaties van een Nederlands revalidatiecentrum (zie tekstvak 7).

Tekstvak 7: Pilot procedures van LAKA tijdens multidisciplinaire revalidatie

Via e-mail ontvingen patiënten een link naar een pagina over LAKA. Deze pagina was onderdeel van een bestaande beveiligde patiënten portaal dat patiënten al gebruikten om vragenlijsten in te vullen. De speciale pagina over LAKA bevatte stapsgewijze instructies voor: (1) toestemming voor het verzamelen en verwerken van data en (2) het gebruiksklaar maken van LAKA voor gebruik op de eigen computer met Windows besturingssysteem (door installatie na downloaden of vanaf een DVD). Via een e-mailadres en telefoonnummer had men toegang tot centrale technische ondersteuning. Er werden geen expliciete verwachtingen over doelmatigheid van LAKA gedeeld en geen advies gegeven over de mate waarin men de game zou moeten spelen. Ook hadden directe zorgverleners geen formele rol in ondersteuning bij het gebruik van LAKA.

De kwantitatieve data bestonden uit: (1) voor het revalidatieprogramma routinematig verzamelde demografische en gezondheidsgegevens van patiënten, (2) gestructureerde vragenlijstmetingen over acceptatie van LAKA (percepties en intenties) voor en na 8 weken van gebruik en (3) geautomatiseerde registraties van gebruik. Op basis van deze data werd samenhang verkend tussen patiëntkenmerken, percepties, acceptatie en daadwerkelijk gebruik. Vervolgens werden er, op basis van een lijst met thema's, interviews gehouden met een gerichte selectie van patiënten om opvallende patronen van meer uitleg te kunnen voorzien.

Van de 410 in aanmerking komende patiënten, konden er **resultaten** worden opgemaakt van 116 patiënten die aan aanvullende gegevensverzamelingen deelnamen. Daarvan rapporteerden 108 patiënten een problematische mate van vermoeidheid en 47 matig of ernstig intense pijn. Het mediane niveau van bereidheid om LAKA te gebruiken was gematigd positief en nam in de tijd af. Twintig patiënten speelden LAKA van begin tot eind. Met kwalitatieve gegevens kon bevestigd worden dat hedonistische motivatie (ervaren plezier) de belangrijkste factor was voor de acceptatie van LAKA. Bovendien duidden zowel opvallende associaties als citaten van geïnterviewde patiënten op het belang - voor de acceptatie en initiatie van (vrijwillig) gebruik - van coping stijlen van actief aanpakken en zoeken van sociale steun bij problemen. De op gedragsverandering gerichte inhoud werd erkend en als potentieel nuttig ervaren door respondenten die zich aan de inhoud van LAKA blootstelden.

Op basis van deze bevindingen werd **geconcludeerd** dat variatie in vraag naar LAKA tijdens de pilotstudie over het algemeen verklaard werd door percepties over plezier en gemak en individuele verschillen in coping stijl. Een serious game kan volgens patiënten worden aangeboden als een mogelijk aanvulling op multidisciplinaire revalidatie voor patiënten met complexe chronische pijn of vermoeidheidsklachten: wanneer het beter ingebed wordt in bestaande routines van het revalidatieprogramma. Op basis van verbeterde specificaties konden uitvoerbaarheid en effectiviteit in het vervolg op grotere schaal geëvalueerd worden.

9.3.3 Protocol voor uitkomsten- en procesevaluaties

Het 4e hoofdstuk beschrijft een studieprotocol voor uitkomsten en procesevaluaties van serious gaming tijdens multidisciplinaire revalidatie. Daarmee kunnen antwoorden gegeven worden op de **eerste en derde onderzoeksvragen** over: in hoeverre serious gaming de gezondheidsresultaten van patiënten verbetert tijdens reguliere multidisciplinaire revalidatie, maar ook hoe, voor welke patiënten, en onder welke omstandigheden.

Het hoofdstuk beschrijft een ‘ingebedde experimentele gemengde **methoden** ontwerp’ waarin prioriteit werd gegeven aan een 2-armig natuurlijk quasi-experiment. Dat wil zeggen dat er een experimentele groep werd samengesteld

met patiënten die een 4 uur durende 'blended' serious gaming interventie volgden tijdens een intensief multidisciplinair programma op twee locaties van een Nederlands revalidatiecentrum (tekstvak 8). 'Blended' duidt op een combinatie van interventie via de computer en direct contact met zorgverleners. Patiënten in de controlegroep volgden hetzelfde programma zonder serieus gaming onder vergelijkbare omstandigheden op twee andere zorglocaties. Op basis van informatie van de ontwikkelaars, het haalbaarheidsonderzoek en uit de literatuur werden ideeën verzameld voor het ontwikkelen van een realistische programmatheorie. In die fase van het onderzoek werd een onderscheid gemaakt tussen:

- 'Uitkomsten': coping vaardigheden waaraan interventies met een vergelijkbare benadering als LAKA kunnen bijdragen en verbetering in relevante uitkomsten voor patiënten met chronische pijn of vermoeidheid. Hierbij werd onder andere verwacht dat wat patiënten kunnen leren van LAKA betrekking heeft op vaardigheden die vallen onder het containerbegrip 'mindfulness': (neuro)cognitieve processen met betrekking tot zelfbewustzijn, zelfregulatie en 'zelfoverstijging'.
- 'Mechanismen': specifiek spelgedrag of affectieve of motiverende ervaringskwaliteiten die computergames kunnen uitlokken (gevoel van 'aandachtige' en 'realistische' aanwezigheid in een virtuele omgeving, positieve en negatieve emoties)
- 'Context': Uiteenlopende bevorderende of belemmerende factoren bij de implementatie van nieuwe gezondheidsinterventies.

Op basis hiervan werden keuzes gemaakt over benodigde informatie uit: (1) patiëntendossiers (over demografie, diagnostiek, gezondheid en mindfulness uitkomsten en geregistreerd interventiegebruik) en (2) aanvullende feedback vragen over serious gaming m.b.t. acceptatie en ervaringskwaliteiten (positieve en negatieve emoties en sensaties van virtuele aanwezigheid).

Tekstvak 8: Interventies tijdens de eindevaluatie

De multidisciplinaire revalidatiebehandeling

Het 16 weken durende biopsychosociale multidisciplinaire revalidatieprogramma was toegankelijk voor patiënten die voldeden aan de volgende inclusiecriteria: 18-67 jaar oud, langer dan 6 maanden pijn of last van vermoeidheidsklachten of een ziekte aan het houding en bewegingsapparaat gedurende meer dan 3 maanden, geen indicatie voor een andere, meer kosteneffectieve behandeling en gelijktijdig psychosociale problematiek (complexiteit).

Uitsluitingcriteria waren: psychiatrische symptomen die niet voldoende onder controle zijn, risico op psychische decompensatie door een revalidatiebehandeling, taal- of communicatieproblemen die het onmogelijk maken om revalidatie te volgen, of aantoonbaar onvermogen om gedrag te veranderen (bijvoorbeeld als gevolg van persoonlijkheidsstoornissen, aansprakelijkheid van derden, of anders). Er zijn geen aanvullende computervaardighedencriteria toegepast voor deelname aan deze studie.
Het revalidatieprogramma richtte zich vooral op verbetering van psychisch welbevinden en deelname aan sociale rollen. Onder toezicht van een revalidatiearts kregen patiënten gemiddeld 100 uur behandeling; één-op-één of in groepsverband van een team van 2 fysiotherapeuten en 2 geregistreerde psychologen met een masterdiploma. De wekelijkse intensiteit varieerde tussen 3 en 7 uur, afnemend met een toename van sociale rolparticipatie gedurende het hele programma. Over het algemeen ontvingen patiënten 38% fysiotherapie, 30% bevordering van psychisch welbevinden, 23% (andere soorten) psychotherapie en 9% activering en counseling in sociale rolparticipatie. De verschillende interventies werden centraal toegewezen, op basis van individuele onderzoeksresultaten over fysieke status, psychologische en posttraumatische stress, coping, cognitie en psychische welzijn. Het basisprogramma bevatte ook sessies vanuit dezelfde benaderingen als LAKA, gericht op mentale vaardigheidstraining en inschatting van het eigen psychisch welzijn (inclusief optionele 2-daagse training voor patiënten zonder een hoog welzijnsniveau).

Blended (mindfulness-based) serious gaming interventie
LAKA werd geschikt gemaakt voor gebruik op een tablet PC (te downloaden via de Apple en Google-stores). In navolging van haalbaarheidsonderzoekresultaten werd er professionele ondersteuning en gelegenheid geboden om LAKA op de zorglocaties te spelen. Geschikte ruimtes met een Wi-Fi verbinding, tabletcomputers met LAKA geïnstalleerd en een koptelefoon werden gefaciliteerd. Vier serious gaming sessies van één uur werden gepland voor 1 tot 6 patiënten in weken 9-12 van het revalidatieprogramma, aansluitend met andere therapiesessies. Ervaren zorgprofessionals (een fysiotherapeut en 3 psychologen) ondersteunden de 1e introductiesessie en instrueerden om het spel zelfstandig uit te spelen tijdens sessie 2 en 3. Ook verzorgden zijn de vierde sessie: een debriefing met als doel om ervaringen te bespreken en overdracht van het leren naar het dagelijks leven gemakkelijker te maken.

Kwalitatief onderzoek bestond uit focusgroepen met belangrijke betrokkenen, open feedback van deelnemende patiënten en zorgverleners en half gestructureerde patiëntinterviews. Geschat werd dat voor een redelijke kans op een zichtbaar effect er tijdens de onderzoeksperiode genoeg instroom zou moeten zijn om van 250 patiënten de voor- tussen en nametingen te kunnen analyseren (zie tekstvak 9). Voor de analyses werd rekening gehouden met beschikbaarheid van routinematige uitkomstenmetingen op basis van valide instrumenten voor huidige pijnintensiteit, vermoeidheid, pijn coping en cognitie (catastroferen) en psychische symptomen.

Tekstvak 9: Bepaling van de steekproefgrootte

Schattingen van benodigde steekproefgrootte waren gebaseerd op diverse aannames over: aantallen patiënten die niet zouden deelnemen of uitvallen tijdens het onderzoek (20%), effectgrootte (klein tot middelgroot), aanvaardbare kans op een type-II fout (β=0,8), overschrijdingswaarde (α=0,05), aantallen uitkomstenvariabelen (5), controlevariabelen (3) en analysemethode. Ook werd rekening gehouden met het risico dat er belangrijke variatie zou kunnen zijn in uitkomstenpatronen tussen behandellocaties, maar informatie uit de pilot wees erop dat dit onwaarschijnlijk was.

Het onderzoeksprotocol werd goedgekeurd door de ethische commissie van de Tilburg School of Social and Behavioral Sciences en voorafgaand aan inclusie van de eerste patiënt ingevoerd in het Nederlandse trial register (NTR6020).
Het hoofdstuk eindigt door te wijzen op de enerzijds innovatieve en anderzijds inherente beperkingen van de onderzoeksmethoden (tekstvak 10).

Tekstvak 10: Inherente beperkingen aan de pragmatische onderzoeksopzet

Praktische beperkingen sluiten bepaalde keuzes m.b.t. versterking van interne of externe validiteit uit, waaronder: keuze over de controle condities, willekeurige toewijzingen van de interventie aan deelnemers, werving van andere gezondheidscentra, wenselijke diagnostische- en meetmethoden (andere instrumenten en lange-termijn follow-up). Met de pragmatische aanpak verschoven de sterktes van het onderzoek naar kwaliteiten ter beantwoording van procesvragen. Realistische evaluatieprincipes en gemengde methoden worden steeds meer als complementair gezien: geschikter dan een gecontroleerd experiment om programmatheorieën te ontwikkelen ter versterking van overdraagbaarheid van inzicht over variërende interventie-effecten tussen patiënten en instellingen in de gezondheidszorg.

9.3.4 Uitkomstenevaluatie

Hoofdstuk 5 presenteert bevindingen van uitkomstenevaluaties die betrekking hebben op **onderzoeksvraag 1**. De exacte vraag was: wat zijn de mate en opzichten waarin serious gaming tijdens de reguliere multidisciplinaire revalidatie kan bijdragen aan (1) fysiek en emotioneel functioneren in het algemeen, (2) bepaalde uitkomstdomeinen, (3) globale indrukken van patiënten van verandering, algemene gezondheid en functioneren en (4) wat is de invloed van therapietrouw op de effecten van serious gaming?

De studie**methoden** werd uitgevoerd volgens het protocol waarbij de serious gaming interventie werd ingezet tijdens week 9-12 van het revalidatieprogramma (zie tekstvak 11 voor relevante details over de werving en dataverzameling).

Automatische registraties werden gebruikt om subgroepen vast te stellen naar mate van therapietrouw. Statistische modellen werden gebruikt (met behulp van SPSS) om verschillen in gemiddelde uitkomsten te schatten tussen de onderzoeksgroepen en subgroepen in verloop van tijd (zie tekstvak 11; analyseplan).

Tekstvak 11: Relevante details over de uitvoering van de uitkomstenevaluatie

Werving en dataverzameling

Patiënten met een indicatie voor multidisciplinaire revalidatie van een revalidatiearts werden vanaf het begin van de tweede helft van hun revalidatieprogramma (juli-november 2016) door eigen zorgverleners benaderd voor deelname aan het onderzoek. Deelname betekende voor patiënten dat hun gecodificeerde klinische diagnostische en uitkomstgegevens (voor, tussentijds na 8 weken, of na de behandeling van 16 weken) verwerkt werden en dat ze mogelijk benaderd kon worden voor een interview. Alleen kandidaten uit de interventiegroepen werden onmiddellijk na een debriefing ook gevraagd om feedback te geven. Informatiebrieven bevatten geen verwachtingsvormende uitspraken over effecten van serious gaming of parallelle groepsvergelijkingen. Na serious gaming werden feedbackgegevens beschikbaar gesteld aan de onderzoekers om het gelijktijdige kwalitatieve onderzoek te ondersteunen, maar de routinematig verzamelde klinische (diagnostische en uitkomst) gegevens niet.

Analyseplan

Met een multi-level model van herhaalde metingen werd een schatting gemaakt van het groepseffect op de gelijktijdige veranderingen over week 8 tot week 16 in de 4 primaire uitkomstenvariabelen. Vergelijkbare modellen werden gebruikt om uitkomsten apart te schatten voor enkele uitkomsten waarvoor het, op basis van interviews, plausibel was dat deze door serious gaming beïnvloedt kunnen worden. In het bepalen van uiteindelijke uitkomstenmodellen werd rekening gehouden met invloeden van geobserveerde potentieel verstorende factoren. Student t-testen werden gebruikt om secundaire uitkomsten (algemene indruk van verandering, algemene gezondheid, functioneren en tevredenheid over de behandeling) tussen de groepen te vergelijken. Automatische registraties werden gebruikt om subgroepen vast te stellen naar mate van therapietrouw met behulp.

De **resultaten** toonden dat van de 329 in aanmerking komende patiënten die tijdens de onderzoeksperiode instroomden, er 156 interventiegroep en 119 controlegroep patiënten (N = 275) deelnamen aan deze studie. Zij hadden voornamelijk last van chronische rugpijn en psychosociale problemen. 119 patiënten speelden meer dan driekwart van LAKA. Voor de 4 primaire uitkomsten gezamenlijk werd tussen de interventiegroep en de controlegroep een zeer kleine additionele afname (0,119 van een standaarddeviatie met een P waarde van 0,009) geobserveerd tussen de tussentijdse en achterafmetingen van

gezondheidsklachten. Ook vertoonde de interventiegroep een grotere afname in depressieve stemming maar niet in "insufficiëntie" of concentratieproblemen. Er werden geen statistisch significante groepsverschillen gevonden in secundaire uitkomsten. De therapietrouw was over het algemeen vrij hoog en onveranderlijk waardoor het effect ervan niet kon worden vastgesteld.

Uit de bevindingen van dit onderzoek kon **geconcludeerd** worden dat er een zeer klein gemiddeld effect op primaire uitkomsten is van aanvullende serious gaming tijdens multidisciplinaire revalidatie. Enerzijds is een effect in deze beperkte orde van grootte alleen statistisch en niet klinisch significant. Anderzijds kunnen de resultaten een indicatie zijn dat serious gaming een relatief tijd-efficiënte behandelcomponent zou kunnen zijn. Dit verdient nader onderzoek naar wanneer, hoe en voor welke patiënten versterking van een behandeling met serious gaming kosteneffectief is en waarom.

9.3.5 Procesevaluatie

Hoofdstuk 6 bevat procesevaluaties voor het beantwoorden van **onderzoeksvraag 3** over hoe serious gaming tijdens multidisciplinaire revalidatie zou kunnen werken, waarom, voor wie, en in welke feitelijke behandelingsomstandigheden. Het doel was om antwoorden te geven in de vorm van een overdraagbare 'programmatheorie'.

Aanvullende **methoden** van procesevaluatie werden voor, tijdens en na het tweearmige natuurlijke quasi-experiment ingebed. Voor inspectie van uitkomstgegevens werden de uitgewerkte transcripten van focusgroepen met lokale belanghebbenden en half-gestructureerde patiëntinterviews gecodeerd. Daarbij werden configuraties vastgesteld van ‘interventiekenmerken (I) in context (C) die mechanismen (M) activeren voor het produceren van uitkomsten (O)’. Vervolgens werden hypothesen geformuleerd en getoetst aan kwantitatieve gegevens met behulp van multipele regressie- en (gemodereerde) mediatie modellen (zie hoofdstuk 6). Uiteindelijk werden er proposities geformuleerd op basis van initiële en aanvullende kwalitatieve bevindingen voor zover deze ondersteund en niet verworpen werden door kwantitatieve bevindingen.

Kwalitatieve **resultaten** maakten zichtbaar dat ervaren zelf-discrepanties door patiënten tijdens serious gaming een noodzakelijke trigger (M) waren om te leren zelfbewuster te zijn in momenten van dagelijkse sociale interactie (O). Productieve spelervaringen kunnen daarom op basis van de zelfdiscrepantie theorie uitgelegd worden (hoofdstuk 6, tekstvak 3). Er werden diverse kenmerken van interventie in context geïdentificeerd die voor acceptatie of leerresultaten van belang zouden kunnen zijn.

Tekstvak 12: Interventie – context – mechanisme – uitkomsten configuraties voor acceptatie en leerresultaten van serious gaming tijdens (multidisciplinaire revalidatie)behandeling

ICMOC 1: Acceptatiepercepties na serious gaming zijn lager wanneer:

- ontwerpkwaliteiten met betrekking tot feedback en aanpassing aan de voorkeuren van de ontvanger beperkt zijn;
- een patiënt die het gebruikt van een hogere leeftijd is (C), en;
- als implementatieprocessen (d.w.z. planning en ondersteuning) binnen verantwoordelijke organisatie-eenheden niet getrouw zijn in het bieden van onmiddellijke debriefing

ICMOC 2: Meer zelfbewustzijn in het dagelijks leven en daaropvolgende veranderingen in gezondheidsuitkomsten (rehabilitatieresultaten) kunnen uitgelokt worden met serious gaming-taken die patiënten bewust maken van discrepantie tussen 'zelf-scripts' en het 'feitelijk zelf' en emotionele gevolgen daarvan als:

- het een relatief voordelige innovatie is (voor ervaringsleren) en past in de rationale van het behandelingsprogramma;
- de patiënt weinig neiging heeft om actief of veelzijdig (beheersmatig) om te gaan met stress of pijn en;
- organisatorische implementatieprocessen gekenmerkt worden door een adequate planning voor de patiënt: behoefte aan het leerdoel is actueel en debriefing wordt gevolgd in een kleine groep met andere patiënten.

Kwantitatieve resultaten toonden dat de zeer kleine verschillen in verandering tussen de studiegroepen in zelf-gerapporteerde depressie, pijn en vermoeidheidsveranderingen 'gemedieerd' werden door kleine groepsverschillen in mindfulness verandering. Meer mindfulness verandering ging ook samen met een hogere mate van aandacht van de patiënt voor de virtuele wereld van LAKA ($n = 114$, $\beta = 0{,}36$; $P = 0{,}001$). Acceptatie van serious gaming was lager bij oudere patiënten. Uitkomstveranderingen waren sterker bij patiënten die minder actief of veelzijdig (beheersmatig) omgaan met stress of pijn. Mindfulness verandering

en acceptatie varieerden ook met procesindicatoren over variatie door lokale planning en ondersteuning van serious gaming. Hieruit werden 'ICMOCs' geformuleerd voor acceptatie en leerresultaten (zie tekstvak 12)

Deze procesevaluatie **concludeerde** met een voorlopige programmatheorie over hoe, waarom en bij welke patiënten en feitelijke behandelomstandigheden serious gaming een aanvullende hulp kan zijn voor leren over omgaan met - en vermindering van lasten van - chronische pijn of vermoeidheidsklachten (zie hoofdstuk 6, figuur 5).

9.4 ANTWOORDEN OP DE ONDERZOEKSVRAGEN

9.4.1 Effectiviteit van computer gebaseerde interventies waaronder serious gaming tijdens multidisciplinaire revalidatie (vraag 1)

Uit het onderzoek kan geconcludeerd worden dat effecten van computerinterventies op fysiek en emotioneel functioneren van patiënten met chronische somatische symptomen over het algemeen positief en duurzaam zijn, maar ook klein en inconsistent. De bevindingen van dit onderzoek suggereren dat een serious gaming interventie tijdens multidisciplinaire revalidatie een wel statistisch maar niet klinisch significante gezondheidswinst oplevert (met depressie als meest plausibele domein). In vergelijking met eerdere studies naar computerinterventies onder enigszins vergelijkbare omstandigheden is dit resultaat niet uitzonderlijk, maar wel hoopgevend. Hoewel de conclusies gebaseerd zijn op onderzoek met adequate omgang, is er nog wel het nodige te verbeteren aan de onderzoekskwaliteit.

9.4.2 Waarom en voor wie (en wanneer) serious gaming haalbaar is (vraag 2)

Door goede planning en ondersteuning als geïntegreerd onderdeel van een regulier multidisciplinair revalidatieprogramma kan serious gaming een implementeerbare en bruikbare interventie zijn. Er was een opvallend goot verschil in de aantallen patiënten die startten en stopten met gebruik van LAKA tussen (1) de pilotstudie waarin het aangeboden werd zonder ondersteuning van zorgverleners voor thuisgebruik vanaf de eerste week van het revalidatieprogramma en (2) de eindevaluatie waarin gelegenheid tot 'blended' serious gaming in de kliniek werd geboden vanaf week 9. Uit procesevaluaties in beide onderzoeksfasen konden de volgende factoren geïdentificeerd worden voor

acceptatie, het daadwerkelijk starten, of continuering van serious gaming door patiënten:

- Verwachtingen en ervaringen van plezier
- Leeftijd gerelateerd (initiële) aarzeling of angst over het gebruik van de technologie en ervaren moeite tijdens het gebruik;
- Mate va actieve coping stijl en daarmee samenhangende percepties van interne controle en gemak bij het gebruik van de technologie.
- Bestaande gewoonte om computers of games te gebruiken
- Tijdige gelegenheid om spelervaringen met anderen te bespreken.

(Deels) vermijdbare belemmerende factoren hadden betrekking op de personalisatiemogelijkheden binnen het ontwerp van LAKA. Onvermijdbaar lijken belemmeringen voor patiënten met zintuiglijke handicap en door noodzakelijke wachtwoordbeveiliging.

9.4.3 Hoe, waarom, voor wie en wanneer computer- en gaming gebaseerde gedrag verandering ondersteuning effectief is

Veranderingen van gezondheidsaspecten die aan computerinterventies toe te schrijven zijn ontstaan;

- door aandachtig gebruik van ondersteuningsmiddelen voor cognitieve en gedragsmatige verandering (hoe) en;
- omdat men een betere omgang ontwikkelt met lichamelijke, persoonlijke en omgevingsomstandigheden, zoals minder piekeren, catastroferen, of vermijden, of meer acceptatie of zelfbewustzijn (waarom);

De consistentie en sterkte waarmee deze veranderingen geactiveerd worden is waarschijnlijk afhankelijk van:

- beschikbare alternatieven (een gunstiger effect wanneer een patiënt computerinterventie wenst voor toegang tot ondersteuning die men anders niet kan ontvangen);
- kenmerken van de patiënt (betere effecten voor wie negatieve emotionele consequenties, zoals depressieve stemming, of lage beheersing bij stress of pijn ervaart) en;
- kenmerken van de interventies in context (relatief voordelige functionele of organisatorische kenmerken, zoals begeleiding door getrainde zorgprofessionals, immersieve technologie om aandacht van patiënten vast te houden, stimulans tot leren uit nieuwe ervaringen).

9.5 AANBEVELINGEN

Tot besluit beschrijft deze samenvatting meerdere aanbevelingen. Specifieke aanbevelingen voor vervolgonderzoek zijn te vinden in tekstvak 13.

Tekstvak 13: Aanbevelingen voor vervolgonderzoek

Toekomstig onderzoek kan toelichten welke bevindingen uit dit proefschrift feilbaar, uitbreid en verfijnd kunnen worden en overdraagbaar zijn bij toekomstige inzet van serieuze gaming onder diverse omstandigheden. Dit ondersteunt toekomstige beslissingen over ontwerp, toewijzing en personalisatie van serious gaming voor optimale kansen voor patiënten op belangrijke gezondheidsvoordeel. Replicatie of weerlegging kan gericht zijn op het aanvullen van methodologische beperkingen die in dit proefschrift aan bod zijn gekomen. Uitbreiding kan gericht worden op een breder scala aan uitkomsten, waaronder kosteneffectiviteit en bereik (opschaling naar patiënten en instellingen). Het betrekken van (vertegenwoordigers van) belanghebbende patiënten, zorgverleners, aanbieders, ontwikkelaars en beleidsmakers bij het richting geven van dergelijk onderzoek is belangrijk om in de toekomst veel patiënten te kunnen bereiken.

Daarnaast worden meer realistische benaderingen aangemoedigd, d.w.z. meer theorie en context gerichte evaluaties van (technologische) innovaties van complexe biopsychosociale interventies. Toekomstige gerandomiseerde experimenten zullen vooral nuttig zijn als zij zich, met de nodige methodologische kwaliteitsverbeteringen, richten op het toetsen van relaties tussen biopsychosociale interventiestrategieën en uitkomsten vanuit grondig begrip over onderliggende mechanismen en activerende condities daarvoor.

Aan patiënten wordt aanbevolen om voor gebruik van een computerinterventie, waaronder "serious gaming", te overwegen of het programma;

- gevolgd kan worden op een computer die men al regelmatig gebruikt;
- begeleiding biedt door deskundige zorgverleners via e-mail of telefoon;
- voldoende stimuleert om de interventie af te maken en om nieuwe perspectieven en gedrag onder uitdagende omstandigheden uit te proberen.
- doelen heeft in opzichten waar persoonlijk belangrijke winst te behalen is.

Op zichzelf kan een computergame kortdurende verlichting van stress of leuke uitdaging bieden.

Zinvolle overwegingen voor zorgverleners kunnen zijn:

- Kijk of computerinterventies onder lokale omstandigheden relatieve voordelen kan bieden voor zelfstandige betrokkenheid van patiënten bij de behandeling en efficiënter gebruik van contacturen.

- Besteed aandacht aan ondersteuning aan patiënten die moeite ervaren bij aanvang van serious gaming, omdat het mogelijk juist een indicatie is van potentie om ervan kan leren.

Organisaties die patiëntenzorg aanbieden kunnen een serious gaming aanpak zoals LAKA adopteren en verder ontwikkelen als een relatief voordelig (niet-overvloedig) programmaonderdeel om patiënten te motiveren tot effectieve zelfbewustzijn oefening voor omgang met emotionele situaties in het dagelijks leven. Ter bevordering van implementatie kan het relatieve voordeel van veilig ervaringsgericht leren worden benadrukt. Voor planning en faciliteiten is het belangrijk om: aan te sluiten bij bestaande routines van patiënten en zorgverleners, technische problemen te voorkomen (wifi, wachtwoordbeveiliging, etc.) en 'debriefing' door een zorgverlener onmiddellijk na het spelen te organiseren met gelegenheid om gaming ervaringen met andere patiënten te delen.

Ontwikkelaars kunnen op basis van de bevindingen uit dit proefschrift een verbeterde versie van mindfulness gebaseerde serious gaming ontwikkelen. Echter, alleen een samenwerkend netwerk van belanghebbende publieke en private organisaties, waaronder vertegenwoordigers van patiënten en hulpverleners, zorginstellingen, zorgverzekeraars, autoriteiten, bedrijven, kennisinstellingen, kan de benodigde voorwaarden scheppen voor het langdurig en grootschalig inzetten.

BRIEF SUMMARY / KORTE SAMENVATTING

BRIEF SUMMARY

Computer games are not in themselves healthy or unhealthy. Virtual rewards in games and social interactions around them determine the "real" meaning of play. So-called "serious games" aim not only to offer fun, but also new knowledge, behavioural change, or mental health improvements. For example, the game "LAKA" was designed to motivate self-awareness training in social and emotional challenges. This may be helpful in dealing with chronic somatic complaints such as pain.

About 1 in 5 Europeans suffer from pain that lasts longer than 6 months. Chronic pain demands attention and challenges life adaptation. If psychological and social problems arise, this leads to high burdens for individuals and societies. "Biopsychosocial" health approaches assume the unity of biological, psychological and social processes. Based on this principle, psychotherapeutic treatments and multidisciplinary rehabilitation programs provide, by estimation, modest and varying health benefits for patients with chronic physical complaints. Computer technology will be important in the future to improve the accessibility and effectiveness of this type of care.

This PhD research focuses on the extent to which the use of computer applications, such as the internet, mobile apps, or a computer game, is effective in reducing the burden of chronic physical symptoms. For users and developers, we also investigated how and why it works for which patients and in which circumstances of care provision.

A systematic literature review identified previously reported experiments with computer-based interventions for patients with chronic pain or unexplained chronic physical complaints. Meta-analyses provided pooled estimates for the average effects on physical symptoms, quality of life, functional interference, cognitions and depression: both immediately after treatment and at least 6 months afterwards. Further exploration of group differences showed possible variation in effects between different comparison conditions, study quality, computer interventions and participating patients.

In feasibility studies, LAKA was made accessible to patients during a multidisciplinary rehabilitation program. Via a web page or DVD they could obtain the game for non-committal usage at home. Coded data from patient records, additional questionnaires, automatic log-data of usage and patient interviews

provided insights to explain striking differences in acceptance and use between different patients. The insights obtained were used to set up a natural experiment, a comparing developments of experienced pain intensity, fatigue, catastrophizing, and psychological complaints between 2 groups of patients: (1) a group of 2 care locations that received a 4-hour serious gaming intervention with LAKA in addition to 100 hours multidisciplinary rehabilitation and (2) a group that received the same intensive rehabilitation program without serious gaming at 2 other locations. Prior to statistically testing the quantitative outcomes, qualitative analyses provided insight into how, why, for whom and under what conditions serious gaming would be acceptable, educational and effective.

The findings from the dissertation suggest that computer interventions have positive and lasting, but also small and varying effects on physical and emotional functioning. For additional serious gaming during multidisciplinary rehabilitation, the estimated effects are "very small". This means that many patients hardly notice improvement. Improving trial methods should be the focus in future outcome evaluation studies.

The use of computer or gaming interventions appeared to be dependent on alignment with habits, motivations (convenience and pleasure), problem-solving ability of users, and appropriate modes of intervention delivery in the healthcare context, such as telephone contact during internet interventions or adequate planning and facilitating of serious gaming during multidisciplinary rehabilitation.

Based on the dissertation, it is found to be likely that computer-based intervention leads to psychological improvement through careful use of cognitive behavioural change techniques, as it is taught to ruminate or catastrophize less, or to be more acceptant or self-aware. Opportunities for improvement seem stronger and more consistent for patients with clear needs to reduce their psychological burden (i.e. those who experience depression or little control over stress or pain) and when expert guidance encourages exposure to experiences in social context. Support, refutation, expansion and refinement of these propositions requires future theory-oriented and context-sensitive evaluations.

KORTE SAMENVATTING

Computergames zijn op zichzelf niet gezond of ongezond. Virtuele beloningen in games en sociale interacties er omheen bepalen de 'echte' betekenis voor spelers. 'Serious games' beogen niet alleen plezier te bieden, maar ook nieuwe kennis, gedragsverandering, of mentale gezondheidsverbeteringen. De game 'LAKA' werd ontworpen om te motiveren tot oefening in zelfbewustzijn bij sociale en emotionele uitdagingen. Dat zou behulpzaam kunnen zijn bij het omgaan met chronische lichamelijke klachten zoals pijn.

Ongeveer 1 op de 5 Europeanen heeft pijn die langer dan 6 maanden aanhoudt. Chronische pijn eist aandacht op en daagt uit tot aanpassing. Daarbij kunnen psychische en sociale problemen ontstaan en daarmee hoge individuele en maatschappelijke lasten. Psychotherapeutische en multidisciplinaire revalidatie programma's die uitgaan van de eenheid van biologische, psychische en sociale processen leveren bescheiden en wisselende gezondheidswinst op voor patiënten met chronische lichamelijke klachten. Computertechnologie bieden potentieel om deze zorg toegankelijker, effectiever of goedkoper te maken.

Dit promotieonderzoek richt zich op de vraag in hoeverre inzet van computertoepassingen, zoals het internet, mobiele apps, of computergame, effectief is om lasten van chronische lichamelijke symptomen te matigen. Voor gebruikers en ontwikkelaars is ook onderzocht hoe en waarom het werkt bij welke patiënten en in welke omstandigheden van zorgverlening.

Een systematische literatuurstudie identificeerde eerdere experimenten met door computer ondersteunde interventies voor patiënten met chronische pijn of onverklaarde chronische lichamelijke klachten. Met meta-analyses werden totale schattingen gemaakt van effecten op lichamelijke symptomen, kwaliteit van leven, functionele belemmeringen, cognities en depressie; na de behandeling en minstens 6 maanden later. Verdere verkenning van groepsverschillen toonde mogelijk wisselende uitkomsten tussen vergelijkingscondities, studiekwaliteit, computerinterventies en deelnemende patiënten.

In haalbaarheidsonderzoek werd LAKA eerst toegankelijk gemaakt voor patiënten tijdens een multidisciplinair revalidatieprogramma: via een webpagina of DVD om vrijblijvend thuis te gebruiken. Gecodeerde gegevens uit patiëntendossiers, aanvullende vragenlijsten, automatische gebruiksregistraties

en patiëntinterviews boden inzichten ter verklaring van opvallende verschillen in acceptatie- en gebruik tussen verschillende patiënten.

Daarna werd in een natuurlijk experiment de vergelijking gemaakt in ontwikkelingen van ervaren pijnintensiteit, vermoeidheid, catastroferen en psychische klachten tussen 2 groepen patiënten: (1) een groep van 2 zorglocaties die een 4 uur durende serious gaming interventie met LAKA ontving als aanvulling op 100 uur aan multidisciplinaire revalidatie en (2) een groep die hetzelfde intensieve revalidatieprogramma zonder serious gaming ontving op 2 andere locaties. Voorafgaand aan het statistisch toetsen van de kwantitatieve uitkomsten gaven kwalitatieve analyses inzicht in hoe, waarom, voor wie en onder welke voorwaarden serious gaming acceptabel, leerzaam en doelmatig zou zijn.

De bevindingen uit het proefschrift suggereren dat computerinterventies positieve en blijvende, maar ook kleine en wisselende effecten hebben op fysiek en emotioneel functioneren bij patiënten. Voor aanvullende serious gaming tijdens multidisciplinaire revalidatie zijn de geschatte effecten ‘zeer klein’. Dit betekent dat veel patiënten verbetering niet of nauwelijks opmerken. Verbetering van onderzoeksmethoden dient de focus te zijn in toekomstige effectstudies.

Gewenst gebruik van computer of gaming interventies wordt bepaald door aansluiting bij gewoonten, acceptatie gerelateerde percepties (gemak en plezier), probleemoplossend vermogen van gebruikers en passende aanbiedingswijzen in de zorgverleningscontext, zoals telefonisch contact bij internetinterventies of serious gaming integraal plannen en faciliteren tijdens multidisciplinaire revalidatie.

Op basis van het proefschrift is het aannemelijk dat computerinterventie tot psychische verbetering leidt via aandachtig gebruik van diverse gedragsverandering-technieken, omdat geleerd wordt minder te piekeren of catastroferen, of te accepteren en zelfbewuster te zijn. Kansen op verbetering lijken sterker en consistenter voor patiënten die behoefte hebben om psychische lasten te verminderen (depressie of weinig controle over stress of pijn ervaren) en wanneer deskundige begeleiding aanzet tot blootstelling aan ervaringen in een sociale context. Bevestiging, verwerping, uitbreiding en verfijning van dit beeld vraagt om meer theoriegerichte en contextgevoelige evaluaties.

DANKWOORD

DANKWOORD

Dit proefschrift is geschreven in een tijd dat er steeds meer met computers wordt gespeeld en een tijd waarin het begrip ‘curlingouders’ ontstond. Voor wie niet goed geluisterd heeft naar juf Ank uit de serie ‘de luizenmoeder’: in deze metafoor worden ouders vergeleken met ‘vegers’ in de curlingsport, die met bezems de ijsbaan net voor de glijdende curlingsteen verwarmen, zodat een steen die niet exact de juiste koers volgt minder weerstand ondervindt en toch op de gewenste plaats eindigt. Zo proberen curlingouders uit alle macht hun kinderen voor misstappen en pijnlijke ervaringen te behoeden. Gelukkig zijn Anneriet en Mario Vugts niet zo. Anders hadden mijn meest leerzame ervaringen, waaronder het schrijven van dit proefschrift, nooit plaatsgevonden.

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Mijn allergrootste geluk is Mirte. Je bent gemakkelijk te onderschatten, maar het spreekt voor zich: het grootste deel van de tijd dat we elkaar kennen deed ik promotieonderzoek, hockey liet ik nooit helemaal los en toch trouwde je met me! Gelukkig zijn we beiden overtuigd dat je niet te snel tevreden hoeft te zijn, maar dat we over elkaar niet hoeven te twijfelen. Familiebezoekjes zijn voor ons een goede afleiding. Dus bedankt Christel, Roland, Frans, oma Liesje, Ivette, Saïda, Kim, Diederick, Jeroen, Sydney, Britt, Lana, Bente, Nout en Enzo!

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Voor de ontwikkeling van LAKA kon ik toepassen wat ik in mijn studie organisatiewetenschappen leerde over multidisciplinaire samenwerking. Veel voldoening haalde ik uit het werken met initiatiefnemers Fons en Jan, Jac Geurts (ditmaal als adviseur), gamedesigner Derk de Geus, vormgever Tim Hengeveld en andere tovenaars van Paladin Studio's, scriptschrijver Karel Michiels, projectmanager Joost Volmer, psychometrist Ton Akkerman en ICT adviseur Marcel Lips. Ik bedank hen allen voor de bijdrage van deze periode aan het onderzoek en mijn persoonlijke ontwikkeling.

Mijn Tranzo-vuurdoop als kersverse 'science practitioner' ontving ik tijdens het jaarlijkse teamuitje, dat door Noud en Leonieke in Nijmegen werd georganiseerd. Het was erg leuk en best intens om in één keer met tientallen nieuwe collega's kennis te maken met allerlei vragen over mijn eerste ideeën. Daarop volgden nog vele jaren van veel leuke en/of interessante momenten van kennisdeling, gesprekken (en dansjes) tijdens Tranzo lunches, zorgsalons, werkplaatsbijeenkomsten, uitjes, heidagen, promoties en andere gelegenheden met Henk, Ien, Evelien, Jacqueline, Bert Meijboom, Diana, Mariëlle, Tineke, Loraine, Lieke, Neis, Hilde, Corelien, Sabine, Kim, Carien, Lisette, Jan, David, Nienke. Wie Tranzo kent begrijpt dat het echt onmogelijk is om iedereen op te noemen. Daarom, in het algemeen, dank aan de leiding van Tranzo, bewuste initiatiefnemers en iedereen die met mij aan deze momenten deelnam. Andrea, fijn dat we in contact blijven als buren en in samenwerking aan het project "rookvrij schoolterrein". Jogé, ik denk met bijzonder veel plezier terug aan ons zeer gezellige en productieve bezoek aan Brisbane.

Dankwoord

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CURRICULUM VITAE

Miel Vugts werd geboren op 14 januari 1985 in Breda, Nederland. Hij slaagde voor het Atheneum aan de Katholieke Scholengemeenschap in Etten-Leur. Daarna behaalde hij een bachelor diploma in organisatiewetenschappen en research master diploma in sociale en gedragswetenschappen aan Tilburg University. Na zijn opleiding werkte hij als wetenschappelijk medewerker bij Top-Care en P.R.B. Services aan de ontwikkeling van de game 'LAKA'. In mei 2013 startte hij als 'science practitioner' bij Tranzo, wetenschappelijk centrum voor gezondheid en welbevinden, aan zijn promotieonderzoek. In november 2018 startte hij als postdoc bij Tranzo aan verklarend onderzoek naar implementatie en opschaling van computertoepassingen gericht aan patiënten met Chronische pijn. Sinds 2001 is hij naast studie en onderzoek bijna onafgebroken actief als hockeytrainer en coach.

Miel Vugts was born on January 14, 1985 in Breda, the Netherlands. He passed his secondary education at the 'Katholieke Scholengemeenschap' in Etten-Leur. A bachelor's degree in organizational sciences and a research master's degree in social and behavioural sciences were obtained at Tilburg University. Subsequently, he worked as a scientific employee at 'Top-Care' and 'P.R.B. Services', which included working on the development of the serious game 'LAKA'. In May 2013, he started his PhD research as a science practitioner at Tranzo, scientific centre for health and well-being. In November 2018 he started working as a postdoc at Tranzo to do explanatory research on implementation and scale-up of computer interventions aimed at patients with chronic pain. In addition to his studies and research, he has been active as a field hockey coach since 2001.